

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Design and Evaluation	
Review Completion Date	April 28, 2022
Subject	Evaluation of Need for a REMS
Established Name	Mavacamten
Trade Name	Camzyos
Name of Applicant	Myokardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb
Therapeutic Class	Cardiac Myosin Inhibitor
Formulation(s)	2.5 mg, 5 mg, 10 mg, and 15 mg oral capsules
Dosing Regimen	Starting dose of 5 mg once daily with dose adjustments as outlined in the prescribing information

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for the new molecular entity Camzyos (mavacamten) to mitigate the risk of heart failure due to systolic dysfunction. Myokardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb submitted a New Drug Application (NDA) 214998 for Camzyos with the proposed indication for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) in adults to improve functional capacity and symptoms.¹ The risk associated with Camzyos include heart failure due to systolic dysfunction. The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

The risk of heart failure due to systolic dysfunction associated with Camzyos is serious, severe, and potentially fatal, and can be mitigated by decreasing the dose or discontinuing Camzyos. If decreases in left ventricular ejection fraction (LVEF) to less than 50% occur, the dose of mavacamten will be held for at least 4 weeks. If the LVEF increases to $\geq 50\%$, Camzyos may be restarted at the next lowest dose. If at any time LVEF falls below 50% twice at the lowest dose (2.5 mg daily), Camzyos must be permanently discontinued. The dose of Camzyos must also be decreased to the next lowest dose if a patient begins therapy with a moderate CYP3A4 inhibitor or weak CYP2C19 inhibitor to decrease the potential of drug-drug interactions causing a decrease in LVEF. Due to this, the risk of heart failure due to systolic dysfunction and drug-drug interactions will be included in a boxed warning. While it is expected that cardiologists will be familiar with the symptoms and management of heart failure due to systolic dysfunction, cases of asymptomatic decrease in LVEF, the complexity of appropriate dosing of Camzyos, the need for periodic patient monitoring via echocardiogram, and multiple drug interactions requiring dose adjustment remain of concern. DRM and the Division of Cardiology and Nephrology agree that labeling is not sufficient to mitigate these risks and have determined a REMS with ETASU is necessary to ensure the benefits of mavacamten outweigh its risk of heart failure due to systolic dysfunction and drug-drug interactions.

The goal of the Camzyos REMS Program is to mitigate the risk of heart failure due to systolic dysfunction.

Objectives:

1. Monitor for detections of heart failure due to systolic dysfunction with periodic echocardiograms
2. Screen for drug interactions prior to each dispense

The Camzyos REMS includes the following elements: ETASU A (healthcare providers who prescribe Camzyos are specially certified), ETASU B (pharmacies that dispense Camzyos are specially certified), ETASU D (dispensing of Camzyos may be done only with the documentation of safe-use conditions), and ETASU E (each patient using Camzyos is subject to certain monitoring), an implementation system, and a timetable for submission of assessments. Prescribers must certify and patients must enroll to ensure they are aware of the risk and monitoring requirements, and pharmacies must certify and verify that prescribers are certified, patients are enrolled and authorized to receive Camzyos, and verify that

patients are not on any interacting medications and supplements that require a dose adjustment of mavacamten or discontinuation of the interacting medication.

Dependent upon assessment findings and postmarketing requirements results, FDA may modify the REMS or consider other regulatory actions. FDA may, in the future, determine that certain elements of the REMS, or the REMS in its entirety, are no longer necessary.

1. Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)^a Camzyos (mavacamten) is necessary to ensure the benefits outweigh its risks. Myokardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb (hereafter referred to as “the Applicant”) submitted a New Drug Application (NDA) 214998 for Camzyos with the proposed indication of the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adults to improve functional capacity, (b) (4) and symptoms. The NDA is currently proposed for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms.¹ This application is under review in the Division of Cardiology and Nephrology (DCN). The Applicant’s proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Camzyos outweigh the risk of heart failure due to systolic dysfunction.

2. Background

2.1. Product Information

Camzyos, a new molecular entity, is a first in class cardiac myosin inhibitor, currently proposed for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy to improve functional capacity and symptoms. Camzyos is an allosteric, selective, and reversible inhibitor of cardiac myosin. It is proposed to modulate the amount of myosin heads that can enter “on actin” state, which reduces the systolic (force-producing) and diastolic (residual) cross-bridge formation. This decreases ventricular contractility and relieves left ventricular outflow tract obstruction. Camzyos is primarily metabolized by cytochrome P450 (CYP) 2C19 and CYP 3A4. The half-life of mavacamten is CYP2C19 genotype dependent, but in normal metabolizers, the half-life is 8 days.^{2,3}

Camzyos is proposed to be available as 2.5 mg, 5 mg, 10 mg, and 15 mg oral capsules. The starting dose of Camzyos is 5 mg once daily and may be increased 12 weeks after initiation based on pharmacodynamic (PD) markers (See Section 5). The dose must be decreased based on PD markers and concomitant medications and supplements that may increase the effects of Camzyos (see Section 5 for

^a Section 505-1(a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity*

details regarding posology and monitoring of Camzyos therapy).¹ It is expected to be a long term therapy for adult patients with oHCM.^b Mavacamten is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for Camzyos (NDA 214998) relevant to this review:

- 04/27/2016: Agency granted Camzyos Orphan designation for the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adults to improve functional capacity, (b) (4) and symptoms.⁴
- 07/12/2020: The clinical review team informed the Applicant at pre-NDA meeting that a REMS for mavacamten was necessary to mitigate the risk of heart failure.⁵
- 07/22/2020: Agency granted Breakthrough Therapy designation for the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adults to improve functional capacity, (b) (4) and symptoms.⁶
- 10/06/2020: An informal teleconference meeting was held with Myokardia, the DCN clinical review team, and the Division of Risk Management (DRM) to discuss Myokardia's proposal for (b) (4) REMS. The DCN clinical review team emphasized the need for a REMS ensuring ECHO monitoring was performed.
- 01/28/2021: NDA 214998 submission for the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adults to improve functional capacity, (b) (4) and symptoms received.
- 07/14/2021: A Mid-cycle communication meeting was held between the Agency and Myokardia via teleconference. The Agency informed Myokardia that a REMS was necessary to ensure the benefits of Myokardia outweigh the risk of heart failure due to systolic dysfunction. DRM informed Myokardia that comments on the proposed REMS would be forthcoming once Agency meetings with CDER senior leadership were completed. The Office of Clinical Pharmacy requested dosing and monitoring modeling according to CYP2C19 genotype.⁷
- 08/06/2021: Applicant submitted modeling of exposure-response and pharmacokinetic/pharmacodynamic simulations evaluating different dosing and monitoring protocols in CYP2C19 genotypes in response to the Agency's request on July 14, 2021.
- 09/16/2021: DRM provided comments and redlined REMS materials to the Applicant on the January 28, 2021, REMS submission.⁸
- 09/30/2016: A Discipline Review Letter was issued noting that prospective CYP2C19 genotyping, and a companion diagnostic may be required for optimizing efficacy and reducing risks for poor CYP2C19 metabolizers.⁹
- 10/07/2021, 10/27/2021, 11/02/2021: The Applicant and Agency engaged in discussions regarding the feasibility and appropriateness of prospective genotyping using a companion diagnostic.

^b Section 505-1(a) FD&C Act: *FDAAA Factor (D): The expected or actual duration of treatment with the drug.*

- 11/08/2021: The Applicant submitted a REMS amendment including prospective genotyping as a requirement of the REMS. This constituted a major amendment.
- 11/18/2021: Major amendment acknowledgement letter sent to Applicant: the PDUFA goal date was extended by 3 months to April 28, 2022.¹⁰
- 01/11/2022, 01/12/2022: The Applicant and the Agency discussed the Agency's proposed dosing and monitoring plan and drug-drug interaction management that did not include prospective genotyping. The need to involve stakeholders in the REMS planning to ensure the proposed REMS can be incorporated into practice workflows was also discussed.
- 01/25/2022: The Applicant submitted a REMS amendment that included a REMS proposal that did not include prospective genotyping requirements.
- 02/04/2022: The Applicant submitted their findings of stakeholders' feedback regarding the REMS.
- 03/02/2022: DRM sent Interim Comments and redlined Camzyos REMS materials to Bristol Myers Squibb, with a notification that edits to the Camzyos REMS Assessment Plan would be forthcoming. As part of the redlined REMS materials, DRM sent a new REMS material, the Camzyos REMS *Drug Interaction and Counseling Checklist for Pharmacies*, to address concerns regarding drug-drug interactions with inhibitors of CYP2C19 and CYP3A4 that can contribute to heart failure due to systolic dysfunction. This checklist requires dispensing pharmacists to conduct a screening of all prescription and nonprescription medications and supplements for drug-drug interactions, and counsel the patient. The *Drug Interaction and Counseling Checklist* The Pharmacist Portal must give the dispensing pharmacist the ability to complete the *Drug Interaction and* (b) (4) *Counseling Checklist* online.¹¹
- 03/09/2022: DRM sent an addendum to the March 2, 2022, Interim Comments that included additional comments and a redlined Camzyos REMS *Drug Interaction and Counseling Checklist for Pharmacies* to align with the Division of Mitigation and Medication Error Surveillance (DMAMES) comments and redlined Camzyos Assessment Plan.^{12,13}
- 3/14/2022: DRM, DMAMES, DCN, and Bristol Myers Squibb participated in a teleconference to discuss the Interim Comments sent by the Agency on March 2 and 9, 2022. During this meeting, the Applicant and the Agency aligned on changing the patient enrollment process to include all relevant information including baseline echocardiogram on the Patient Enrollment Form instead of requiring a Patient Status Form to also be submitted, per stakeholder input (b) (4).
 (b) (4) The Agency maintained the position that the REMS, while not intended to replace practice of medicine, is a safety program that is necessary for safe use of the product and would not be able to adequately mitigate the risk if prescribers were allowed to override the safeguards of the program. (b) (4)
 inclusion of echocardiogram information (b) (4) to provide to pharmacists, (b) (4)
 (b) (4) it would improve pharmacy workflow and dosing decision-making, as it provided rationale for dosing changes.
- 03/22/2022: The Applicant submitted a REMS amendment that included their updated REMS proposal and aligned with the Agency's position as discussed on March 14, 2022.

- 04/08/2022: DRM sent Interim Comments and redlined Camzyos REMS materials to Bristol Myers Squibb, with a notification that edits to the Camzyos REMS Document and stakeholder attestations would be forthcoming.¹⁴
- 04/11/2022: DRM sent a Camzyos REMS Document and stakeholder attestations for the Applicant's use.
- 04/13/2022: DRM sent an updated redlined REMS Document and stakeholder attestations along with an email correspondence regarding alignment with BMS' proposal to incorporate the *Drug Interaction and Counseling Checklist for Pharmacies* into pharmacy workflow while maintaining the "hard stop" if the *Checklist* was not completed and submitted.
- 04/18/2022: The Applicant submitted a REMS amendment that included their updated REMS proposal.
- 04/21/2022: DRM sent Interim Comments and redlined Camzyos REMS materials to Bristol Myers Squibb with edits including updates to align REMS materials with the Prescribing Information and heart failure symptoms for patients with the Medication Guide.¹⁵
- 04/25/2022: The Applicant sent an informal email submission of redlined and clean versions of the Camzyos REMS to the Agency prior to the official submission, due to the Agency on Tuesday, April 26, 2022.
- 04/25/2022: DRM sent Comments and redlined Camzyos REMS Document and materials with edits to properly delineate stakeholders in the REMS Document, align the stakeholder attestations with the REMS Document, and align the Word and pdf versions of the *Patient Brochure*.
- 04/26/2022: The Applicant submitted both an informal email submission and an official submission through the gateway of redlined and clean versions of the Camzyos REMS.
- 04/27/2022: The Agency sent redlined edits to figures in Section 2.1 of the Prescribing Information. These figures are reproduced in the Education Program for *Healthcare Providers and Pharmacies* slide deck, and therefore must align with the Signatory's edits to the Prescribing Information.
- 04/27/2022: The Applicant submitted a REMS in response to the 4/27/2022 that aligned with the requested edits to the Prescribing Information and was approvable.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Hypertrophic cardiomyopathy (HCM) is a genetic disorder leading to chronic, progressive disease caused by cardiac myosin sarcomere mutations that increase the calcium sensitivity of myofilaments and may dysregulate sarcomere structure. This favors excess cross bridge formation during both systole and diastole, which results in ventricular hypercontractility due to myocyte hypertrophy, disarray, and fibrosis. Pathophysiological features of HCM include hypercontractility, impaired relaxation, and dynamic left ventricular outflow tract (LVOT) obstruction. It is estimated that 0.2% of the US population has HCM, although the current diagnosis rate is lower due in part to some patients being

asymptomatic.¹⁶ Obstructive hypertrophic cardiomyopathy (oHCM) accounts for approximately 70% of diagnoses of HCM. It occurs when the ventricular septum becomes thickened along with the left ventricle. This obstructs the blood flow from the left ventricle to the aorta, and patients present with an LVOT gradient of ≥ 30 mmHg.² An estimated 2 – 5 per 10, 000 patients^c have symptomatic oHCM.¹⁷ Patients may be asymptomatic, and can go undiagnosed, however when symptoms do occur, they include angina, dyspnea, and syncope. Patients who have oHCM also have comorbidities that include atrial fibrillation.¹⁸ These can lead to increased risk of congestive heart failure, stroke, and death.^d Diagnosis is usually done via an echocardiogram to view the thickened cardiac muscle and may be augmented by a cardiac MRI and findings of abnormal rhythm on an electrocardiogram.

3.2. Description of Current Treatment Options

There are no currently approved disease-specific therapies for oHCM. Per the 2020 AHA/ACC Guidelines for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy, patients are treated initially with nonvasodilating beta blockers, non-dihydropyridine calcium channel blockers, and disopyramide however, they do not always control oHCM symptoms such as angina and dyspnea.¹⁹ Propranolol carries an approved indication for improving NYHA functional class in oHCM. In patients who have atrial fibrillation, warfarin, apixaban, dabigatran, and rivaroxaban may be used to prevent blood clots. None of these medications that target various symptoms of oHCM have any serious risks that warrant a REMS. Other options for treatment are surgical septal myectomy to remove a portion of the thickened septum to improve blood flow, and alcohol ablation, which destroys the thickened portion of the septum with alcohol.²⁰

4. Benefit Assessment

The pivotal phase 3 trial (EXPLORER-HCM, NCT-03470545) supporting this application consisted of a randomized, double-blind, placebo controlled, multicenter international, parallel-group trial which evaluated 251 adult patients with symptomatic NYHA class II and III oHCM with left ventricular ejection fraction (LVEF) $\geq 55\%$, and LVOT peak gradient ≥ 50 mmHg at rest or with provocation. Patients in EXPLORER-HCM were randomized 1:1 to Camzyos or placebo for 30 weeks. The primary composite functional endpoint was defined as achieved with an improvement of pVO₂ by 1.5 mL/kg/min or more and improvement in NYHA class by at least 1, or an improvement of pVO₂ by > 3.0 mL/kg/min or more and no worsening in NYHA class. Secondary endpoints included treatment effects of Camzyos on LVOT obstruction, functional capacity, and health status assessed by change from baseline through Week 30

^c Section 505-1(a) of the FD&C Act: *FDAAA Factor (A): The estimated size of the population likely to use the drug involved.*

^d Section 505-1(a) of the FD&C Act: *FDAAA Factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

in post-exercise LVOT peak gradient, change in pVO₂, proportion of patients with improvement in NYHA class, Kansas City Cardiomyopathy Questionnaire-23 (KCCQ-23) Clinical Summary Score (CSS), and Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) Shortness of Breath (SoB) domain score.

A greater proportion of subjects met the primary endpoint at Week 30 in the Camzyos group compared to the placebo group (36.6% vs 17.2%, respectively, p=0.0005). At Week 30, patients receiving Camzyos had greater improvement compared to placebo across all secondary endpoints. As presented at the REMS Oversight Committee (ROC) meeting on August 4, 2021, the clinical review team concludes that overall, the therapeutic benefit of Camzyos was demonstrated and the benefit can be translated as one per every five Camzyos-treated patients would expect to have some improvements on functional capacity and symptom burden.^e

5. Risk Assessment & Safe-Use Conditions

The safety of Camzyos was evaluated primarily in the pivotal EXPLORER-HCM phase 3 trial and is supported by four other Phase 2 and Phase 2/3 studies of oHCM and nonobstructive hypertrophic cardiomyopathy (nHCM) that include:

- Supporting Phase 2 parent study, MYK-461-004 (PIONEER-HCM, NCT-02842242): an open-label study of efficacy, PD, PK, and safety of Camzyos in subjects with symptomatic oHCM and LVOT obstruction (safety population N = 21).
- Supporting Phase 2 study, MYK-461-006 (MAVERICK-HCM, NCT-03442764): a randomized, double-blind, placebo-controlled study in subjects with symptomatic nHCM (safety population N=56; 39 patients randomized to Camzyos and 19 randomized to placebo).
- Supporting Phase 2/3 extension study, MYK-461-007 (MAVA-LTE): an ongoing long-term safety extension study in subjects with oHCM who completed Phase 3 study EXPLORER-HCM and subjects with nHCM who completed MAVERICK-HCM (safety population N = 180; 137 patients with oHCM and 43 patients with nHCM). The cut-off date for the ISS is May 27th, 2020.
- Supporting Phase 2 extension study, MYK-46-008 (PIONEER-OLE, NCT-03496168): an ongoing open-label extension study in subjects with symptomatic oHCM who were previously enrolled in PIONEER-HCM (safety population N = 13). The cut-off date for the ISS is January 29th, 2020.³

The integrated summary of safety (ISS) is comprised of 330 subjects from the above trials who received at least one dose of study treatment (263 subjects received Camzyos, and 67 received placebo). Of the Camzyos-treated subjects, 209 had a diagnosis of oHCM and 54 had an nHCM diagnosis. At the Agency's request, a 120-day safety update was submitted through May 2021.

Of the 251 patients in the pivotal trial, 123 patients were treated with Camzyos for a median duration of exposure of 30.4 weeks. The most common adverse event in the pivotal trial Camzyos-treated group

^e Section 505-1(a) of the FD&C Act: *FDAAA Factor (C): The expected benefit of the drug with respect to such disease or condition.*

was dizziness (27% vs. 18% in the placebo-treated group). Other common adverse events occurring in >5% of Camzyos-treated subjects were headache, backpain, arthralgia, and syncope.

5.1. Deaths

There was one event of sudden death in the placebo group of the EXPLORER-HCM pivotal trial. With the inclusion of safety data from the May 2021 120-day update, there were 3 deaths in subjects receiving Camzyos in the ISS. Per the ongoing clinical review, this is within the background death rate for the patient population. Review of the narratives did not indicate Camzyos was a contributor in the deaths. One death was attributed to cardiac arrest in the setting of worsening AF and post-procedure AF ablation. Camzyos was continued during the subject's hospitalization, and while the subject's NT-proBNP was significantly increased from 200 pg/mL to 2,800 pg/mL, the subject's LVEF was stable in the 50-55% range. This case raised concern that Camzyos should not be continued in patients who experience worsening clinical status including worsening arrhythmias.²¹ This will be addressed in labeling via the Boxed Warning that states in part, "Interrupt Camzyos if LVEF is <50% at any visit or if the patient experiences heart failure symptoms or worsening clinical status." Of the 2 remaining deaths, one subject's death was attributed to bacteria endocarditis and the other experienced sudden cardiac death.

An overdose death occurred in the long-term extension study MYK-461-007 in the child of a subject. An adult subject was dispensed 15 mg Camzyos capsules, which his 10-month-old son obtained and swallowed 3 (45 mg total) capsules. Within 2 hours, an ICU mobile team arrived at the home, and the 10-month-old was in cardiac arrest and asystole. Extracorporeal cardio-pulmonary resuscitation, extracorporeal membrane oxygenation (ECMO), norepinephrine, milrinone, charcoal chelation, and hemodialysis were all used to treat the infant's overdose. The following day, the infant was transferred to another hospital in worsening condition with signs of severe neurological impairment, multi-organ failure, and no activity on EEG. Rifampicin was administered in an attempt to increase Camzyos clearance but was unsuccessful. One day later, the infant died due to the overdose.^{22,f}

5.2. Heart Failure Due to Systolic Dysfunction

Based on the pharmacologic target of Camzyos, there is a concentration-dependent decrease in LVEF. The increased risk of heart failure due to systolic dysfunction, defined as LVEF < 50%, may result from excessive pharmacologic effect of Camzyos.

Camzyos dosing in the phase 3 trial was designed to avoid excessive pharmacologic effect by titrating the dose based on monitoring of plasma Camzyos concentration (pharmacokinetic [PK] monitoring) and pharmacodynamic (PD) markers including LVEF and LVOT gradient using echocardiography (ECHO). The incidence of heart failure, systolic dysfunction, or LVEF ≤ 30 was 8/314 (2.5%) in the mavacamten group vs 1/147 (0.7%) in the placebo group in the integrated safety data. Of the 8 subjects that experienced a serious heart failure event, six were associated with LVEF dysfunction: four subjects' LVEF dropped

^f Section 505-1(a) of the FD&C Act: *FDAAA factor (E); The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

below 30%, and two subjects' LVEF was < 45%. Overall, the LVEF decline appeared reversible after discontinuation of therapy.³ The clinical review team calculated the number needed to harm is 55 or one out of every 55 Camzyos-treated patients will develop serious heart failure and/or systolic dysfunction.¹⁶

5.2.1 CYP2C19 Metabolizer Status

On August 6, 2021, the Applicant submitted correspondence in response to an Agency request during the midcycle meeting on July 14, 2021 to submit modeling of exposure-response and pharmacokinetic/pharmacodynamic simulations evaluating different dosing and monitoring protocols in CYP2C19 genotypes.²³ This modeling demonstrated that patients who are CYP2C19 poor metabolizers have higher exposures of Camzyos compared to normal, rapid, and ultrarapid metabolizers. When analyzed by the Office of Clinical Pharmacology (OCP), the risk of systolic dysfunction to patients who were poor CYP2C19 metabolizers was indeed greater than that of normal, rapid, and ultrarapid metabolizers.

OCP conducted additional simulations using available population PK and exposure-response models and explored a new dosing algorithm with increased ECHO monitoring frequency, slower up-titration, and without genotyping. The optimized dosing regimen and ECHO frequency offers a similar risk (measured as percentage of patients with LVEF < 50%) and benefit (measured as percentage of patients with VLVOT gradient < 30mmHg) profile compared to the prospective genotyping regimen. Considering that Camzyos is for symptomatic relief, not reduction of mortality, DCN favored this conservative, universal dosing approach.

In the dosing regimen proposed by OCP and used in the Applicant's proposed label,²⁴ the starting dose is 5 mg once daily (Week 0) in all patients irrespective of CYP2C19 genotype. Clinical visits including an echocardiogram are scheduled at Week 4, Week 8, Week 12, and every 12 weeks thereafter. The proposed dosing algorithm allows down-titration at Week 4 and Week 8, if Valsalva left ventricular outflow tract (VLVOT) gradient is less than 20 mmHg. A patient may be eligible for up-titration after 12 weeks (on Week 12, 24, etc.), if VLVOT gradient is (b) (4) 30 mmHg (indicating that desirable efficacy is not reached) and LVEF is (b) (4) 55% (indicating that it is safe to increase dose with available ejection fraction). In addition, the dosing algorithm includes an additional clinical visit with ECHO monitoring at Week 4, Week 12, and every 12 weeks thereafter following any dose adjustment or when restarting treatment after temporary discontinuation ensuring safety at the new dose.

Temporary discontinuation is recommended if ejection fraction drops below 50% at any clinical visit. Patients may resume Camzyos at one lower dose level (i.e., 15 to 10 mg; 10 to 5 mg; 5 to 2.5 mg; once daily) if the ejection fraction returns above 50% at an additional visit 4 weeks after the temporary discontinuation. Permanent discontinuation is recommended if a patient experiences 2 incidences of ejection fraction going below 50% at the lowest dose (i.e., at 2.5 mg once daily) at any time during treatment.

5.2.2 CYP 3A4 and CYP 2C19 Drug Interactions

The above dosing algorithm and monitoring schedule allows for the safe and effective use of mavacamten by patients regardless of metabolizer status. However, due to the issues noted regarding metabolism of Camzyos, the review team further evaluated additional safety concerns regarding drug-drug interactions (DDIs), especially those involving nonprescription medications and supplements. The review team had particular concern for poor metabolizers noting they would also be at greatest risk of systolic dysfunction if Camzyos was taken concomitantly with a drug that further inhibited Camzyos metabolism.²⁵

OCP recommended either to avoid concomitant administration or dose reduction of Camzyos based on the expected magnitude of effect. Concomitant administration of Camzyos with a moderate or strong inhibitor of CYP2C19 as well as a strong inhibitor of CYP3A4 are contraindicated. Due to the number of therapies available and magnitude of pharmacological effect, OCP recommended to decrease the dose of Camzyos and complete ECHO monitoring at Week 4, Week 12, and every 12 weeks thereafter with concomitant administration of Camzyos with a weak inhibitor of CYP2C19 or moderate inhibitor of CYP3A4.²⁵

6. Expected Postmarket Use

Camzyos is expected to be prescribed primarily by cardiologists on an outpatient basis with occasional use in the inpatient setting. In the pivotal Phase 3 trial, subjects' PK (plasma Camzyos concentration and NT-proBNP) and PD (ECHO) data were monitored. In the postmarket setting, clinicians will rely on PD markers only (b) (4). In the post-market setting, it is possible that healthcare providers may not be aware of the risk and need for and frequency of ECHO monitoring with this first in class NME. Patients may miss ECHOs at baseline and at periodic intervals, and therefore may receive Camzyos without the appropriate ECHO monitoring required for the safe use of the drug. The proposed REMS will require that patients are evaluated with periodic ECHO as per labeling, and screening for DDI at each dispense of Camzyos. As a requirement of the REMS, prescribers will complete training, a knowledge assessment, and will enroll in the REMS to become certified to prescribe.

Camzyos' proposed indication is for adult patients with oHCM. While this patient population regularly meets with their cardiac providers, and may have had ECHO and other cardiac evaluations, Camzyos requires ECHO monitoring at more frequent and regular intervals than standard of care for oHCM.¹⁹ As patients with oHCM have an increased risk of heart failure, and will be counseled regarding the risk of heart failure due to systolic dysfunction prior to being enrolled in the REMS and regularly during treatment as required by the REMS, we expect them to be familiar with symptoms of heart failure and seek medical attention if symptoms occur or worsen.

7. Risk Management Activities Proposed by the Applicant

7.1. Review of Applicant's Proposed REMS

To mitigate the risk of heart failure due to systolic dysfunction, the Applicant's initial submission on January 28, 2021, included prescribing information that contained a boxed warning, a Medication Guide (MG) and a REMS with ETASU. The proposed REMS consisted of ETASU that included prescriber certification (A), pharmacy certification (B), documentations of safe use conditions (D), and monitoring (E), an implementation system, and a timetable for submission of assessments of the REMS.

The Applicant's proposed REMS incorporates monitoring based on clinical trial protocols implemented during the clinical development program. In response to Interim Comments and redlined REMS materials from the Agency on September 16, 2021, March 2, 2022, March 9, 2022, April 8, 2022, April 11, 2022, April 13, 2022, April 21, 2022, and April 25, 2022, the proposed REMS was amended on November 8, 2021, January 25, 2022, March 21, 2022, April 18, 2022, April 25, 2022, and April 26, 2022. The final REMS document, REMS materials, and REMS Supporting Document were submitted April 27, 2022. The final Camzyos REMS consists of ETASU that include prescriber certification (A), pharmacy certification (B), documentations of safe use conditions (D), and monitoring (E), an implementation system, and a timetable for submission of assessments of the REMS. Below is an overview of the Applicant's proposed REMS as submitted on January 28, 2021, and amended to include the changes made during the review of the application.

7.1.1. REMS Goals

The Applicant originally proposed the following goal for the Camzyos REMS:



Reviewer's Comments: *The Applicant updated the goals based on comments from the Agency. When determining the goals for the REMS, DRM evaluated how Camzyos will move through the drug use process, potential care gaps, and how the REMS would align with public health prevention goals. DRM identified potential care gaps as the need for periodic ECHO monitoring and the need for drug interaction screening which align with secondary prevention of the risk of HF due to systolic dysfunction. If ECHOs are performed regularly and patients are screened for drug interactions and counseled regularly on signs and symptoms of HF, this may allow HF due to Camzyos to be detected and treated before it becomes severe. The Applicant's other proposals (b) (4) have been removed from the overall goal and objectives of the REMS and will be incorporated as tools to help achieve the goals and objectives.*

DRM concurs with the current proposed goal of the REMS:

The goal of the Camzyos Risk Evaluation and Mitigation Strategy (REMS) Program is to mitigate the risk of heart failure due to systolic dysfunction.

Objectives:

- 1. Monitor for detection of heart failure due to systolic dysfunction with periodic echocardiograms*
- 2. Screen for drug interactions prior to each dispense*

7.1.2. Elements to Assure Safe Use (ETASU)

The Applicant proposed the following ETASU as part of the REMS requirements: prescriber certification (A) pharmacy certification (B), documentation of safe use conditions (D), and monitoring (E).

ETASU A: Prescriber Certification

Prior to prescribing, a healthcare provider (HCP) must certify in the Camzyos REMS. To become certified, healthcare providers must review the prescribing information, the *Program Overview*, and (b) (4) slide deck. The prescriber must then successfully complete and submit the *Healthcare Provider Knowledge Assessment* and *Healthcare Provider Enrollment Form* and submit them to the REMS. Prior to initiating treatment with Camzyos, the prescriber must counsel the patient on the risks, the need for baseline and periodic echocardiogram (ECHO) monitoring, provide the patient with the (b) (4), and enroll the patient in the REMS. Prior to the patient receiving Camzyos and during treatment, the prescriber must assess the results of the ECHO and the patient's cardiovascular status and then determine appropriate action.

Reviewer's Comments: *We agree that HCP certification is necessary to ensure the benefits of Camzyos outweigh the risks. DRM evaluated potential care gaps in the drug use process for Camzyos. We determined that although prescribers are likely to be cardiologists capable of diagnosing and treating heart failure, they may not be familiar with the risk of heart failure in the context of Camzyos prescribing and may not perform ECHO monitoring or DDI screening as directed in the product's labeling which are necessary to ensure safe use. Prescriber certification will ensure prescribers are educated on the drug's serious risks, and that they must adhere to counseling, enrollment, and monitoring of patients, as well as drug interaction screening which supports the goal and objectives of the REMS. An additional component of the prescriber certification will be the completion of a (b) (4) Knowledge Assessment used to further ensure prescribers understand the risks and requirements of the REMS before prescribing Camzyos to patients. While it is expected cardiologists are able to treat heart failure when it occurs, prescribers must be aware of the need to perform echocardiogram monitoring according to the schedule described in Camzyos' label to determine if a patient's LVEF is decreasing while on Camzyos therapy and take appropriate action. The prescriber has the responsibility of assessing the patient's cardiac function and determining the appropriateness of initiating, continuing, or discontinuing treatment. This type of regular ECHO monitoring is not necessary in any other drug for oHCM.*

The Agency conveyed to the Applicant on September 16, 2021, March 2, 2022, April 8, 2022, April 11, 2022, April 13, 2022, April 21, 2022, April 25, 2022, and April 27, 2022, that changes were necessary to the Healthcare Provider directed materials. (b) (4)

(b) (4) upon further review of the NDA, the Agency included a REMS requirement for drug interaction screening be completed at the clinic visit with the HCP, to better inform prescribing of Camzyos. Other recommended changes included changes to the HCP attestations, including the need to screen for drug interactions to support safe use of the product as well as simplifying the introduction and submission information sections on the Healthcare Provider Enrollment Form. We also recommended changes to the (b) (4) to align

with labeling and include case studies to demonstrate dosing and monitoring of Camzyos. DRM provided edits to improve messaging clarity, including streamlining risk messaging from the Prescribing Information, the addition of information on HCP designees and DDIs, removal of inappropriate or potentially confusing graphics, and removal of thumbnail graphics that were not legible. DRM provided edits to the Program Overview to improve formatting, align with labeling and update attestations, and include the need for DDI screening. The HCP Knowledge Assessment also was edited for clarity, to align with labeling, include questions related to DDIs, and to focus questions on information necessary for healthcare providers.

ETASU B: Pharmacy Certification:

The Applicant proposes that Camzyos be dispensed only by certified pharmacies. Pharmacies must become certified by naming an authorized representative who will coordinate REMS activities on behalf of the pharmacy, review training materials and ensure all relevant staff are trained in the REMS to obtain authorization to dispense from the REMS. Pharmacies obtain authorization to dispense by contacting the REMS to verify the patient is enrolled, the prescriber is certified in the REMS and that a current *Patient Status Form* is submitted.

Review Comments: *We agree that pharmacies must be certified prior to dispensing Camzyos to ensure that prior to dispensing, HCPs who prescribe Camzyos are certified and that patients are enrolled and authorized to receive treatment. Authorization to dispense Camzyos is dependent on the successful certification of the HCP prescribing the drug, enrollment of the patient into the REMS, and on completion and submission of the Patient Status Form. The pharmacy is limited to dispensing a 35-day supply.* (b) (4)

DRM proposed a 30-day dispensing limitation throughout the entire time a patient takes Camzyos, as this would reduce the amount of potential excess medication left in homes. Additionally, the dispensing limitation supports more frequent interaction with a healthcare provider. On February 4, 2022, the Applicant submitted a proposal to dispense a 35-day supply to avoid unnecessary interruptions in therapy while echocardiograms are obtained and Patient Status Forms are completed and submitted.²⁶ In DRM'S March 2, 2022 Comments, DRM requested clarification on insurance coverage for a 35-day supply of Camzyos and how pharmacies were expected to dispense a 35-day supply if Camzyos is available in a 30-count bottle. The Applicant responded in the March 21, 2022, REMS amendment that 35 days would be the upper limit of dispensing, and after research of (b) (4), it expected the 35-day dispense to be covered. The Applicant also has a program that patients may elect to use to aid in reimbursement for Camzyos.²⁷ The Applicant included stability data to support a 35 day supply. DRM agrees with this approach.

During the course of the review, while determining how to best mitigate effects on Camzyos metabolism related to a patient's CYP2C19 genotype, the Agency determined it was necessary to screen for DDIs prior to dispensing Camzyos. Camzyos therapy may need to be suspended or require dose adjustment based on DDIs or PD results. To ensure patients' prescription and over the counter

medications and supplements are reviewed for DDI's and to assist with compliance with other REMS requirements, the Agency is requiring the pharmacist to complete and submit the Drug Interaction and (b) (4) Counseling Checklist prior to each dispense of Camzyos. This checklist accounts for medication list review and drug interaction screening, as well as documentation of any dosing changes required after consultation with the prescriber and patient counseling on the risks of Camzyos. If a contraindicated medication or medication that requires dose adjustment is noted on the Checklist and appropriate action is not taken with regards to Camzyos dosing, per the REMS, the pharmacy must not dispense Camzyos.

On September 16, 2021, March 2, 2021, March 9, 2022, April 8, 2022, April 11, 2022, April 13, 2022, April 21, 2022, and April 25, 2022, we provided comments on the pharmacy directed materials and requirements including the need to incorporate the Drug Interaction and (b) (4) Counseling Checklist as a new REMS material. The Applicant clarified the process of how the pharmacy obtains authorization to dispense and who will be contacting prescribers as a reminder to submit Patient Status Forms. The Applicant incorporated the Drug Interaction and (b) (4) Counseling Checklist (b) (4)

(b) (4)

(b) (4)

Because of the expanded pharmacy requirements, additional training was incorporated into the pharmacy certification requirements. Pharmacy authorized representatives must review the Training and complete a knowledge assessment prior to submitting the Pharmacy Enrollment Form. To make the education applicable to both healthcare providers and pharmacy authorized representatives, DRM ensured this education contained information necessary for both stakeholders. DRM also recommended that the Applicant's proposed Pharmacy Authorized Representative Knowledge Assessment include questions targeted to DDIs, necessary monitoring and documentation on the Patient Status Form, align with labeling, and include information on the Drug Interaction and (b) (4) Counseling Checklist. The Applicant incorporated these changes.

ETASU D: Safe Use Conditions

The Applicant proposed to include patient enrollment in the Camzyos REMS to ensure that patients have been counseled by their prescriber on the drug's risks, understand the monitoring requirements and how to recognize signs and symptoms of heart failure due to systolic dysfunction.

Reviewer Comments: We agree with the Applicant's proposal to include patient enrollment. Patient enrollment as a measure of safe use conditions ensures that only patients who have enrolled in the REMS, received counseling from the prescriber, and acknowledge the need for monitoring by getting an ECHO as directed in the Prescribing Information are dispensed Camzyos. We provided edits to the Patient Enrollment Form with updated attestations, inclusion of DDI screening, and removed (b) (4)

(b) (4) We also provided edits to the Patient Brochure to remove (b) (4)

(b) (4)

. A patient-friendly list of commonly interacting prescription and nonprescription

medications and supplements was added to the Patient Brochure, as well as edits to make the list prominent in the Brochure. We also included common symptoms of heart failure as a reminder to patients and updated the brochure globally with patient friendly language.

ETASU E: Monitoring

The Applicant proposed to include cardiovascular monitoring using echocardiogram at baseline and at the frequencies described in the prescribing information. Due to ongoing review of additional safety information and analysis of the magnitude of influence CYP3A4 and CYP2C19 genotype and drug interactions have on Camzyos, the recommended ECHO schedule varied throughout the review timeline.

Reviewer Comments: *We agree that ECHO monitoring is necessary, and after multiple discussions with the clinical team, the frequency that ECHO monitoring must be documented on Patient Status Forms is at Weeks 4, 8, and 12 and every 12 weeks thereafter following dose initiation, 4 weeks, 12 weeks, and every 12 weeks thereafter following a dose change or disruption. We acknowledge that individual monitoring schedules will vary between patients due to potential onset of heart failure symptoms, other cardiac concerns relevant to this patient population, and individualized dose titration.*

Prescribers must complete and submit a Patient Status Form to document that ECHO monitoring was completed, the patient was screened for DDI's, and the patient is authorized to continue therapy with Camzyos. Patient Status Forms must be completed and submitted no later than 3 days after the end of the week the ECHO is due. This allows time for the HCP to complete and submit the Patient Status Form, while also providing the pharmacy enough time to verify the safe use conditions are met to dispense Camzyos. The certified pharmacy will not dispense Camzyos if a Patient Status Form is missing or contains data that is not compatible with continuation of therapy.

Based on the concern related to the quantity and availability of over-the-counter medications and supplements that interact with Camzyos and would require discontinuation of the interacting medication or decreasing the dose of Camzyos, we determined that screening for DDIs at the clinic visit associated with an ECHO by the HCP, as well as screening and documenting prior to dispense by the pharmacy is necessary to ensure safe use of Camzyos. We also concurred with the Applicant on limiting each dispense of Camzyos to no more than a 35-day supply to ensure patients have a grace period between dispenses of Camzyos.

The Agency further determined that Camzyos may not be dispensed if the Patient Status Form indicates that the LVEF < 50%. This ensures patients have met the minimum LVEF requirements in as described in labeling for safe use of Camzyos. We determined that we cannot ensure safe use of Camzyos without this requirement in the REMS. To assist prescribers in dosing decisions and streamline workflow, we suggested including questions regarding LVOT data on the Patient Status Form, which the Applicant incorporated. The responses to the questions on the Patient Status Form will be available in the Pharmacy Portal to assist in dose verification by a pharmacist at a certified pharmacy.

7.1.3. Implementation System

For successful implementation of the REMS, the Applicant proposes to maintain a REMS Call Center and REMS Website to support patients, healthcare providers, pharmacies, and wholesalers to interface with the REMS. The Applicant will notify stakeholders of successful enrollment in the REMS within 1 business day. The Applicant will ensure Camzyos is only distributed to certified pharmacies by wholesalers who are compliant with the REMS requirements. To ensure compliance, the Applicant will develop processes and procedures to maintain adequate records to demonstrate the REMS requirements are being met, as well as a database of all enrolled/certified stakeholders.

Reviewer's Comments: *We agree with the Applicant's proposal to include an implementation system, and provided comments on September 16, 2021, March 2, 2022, March 9, 2022, April 8, 2022, April 11, 2022, April 13, 2022, and April 21, 2022, and April 25, 2022, with additions and edits to the implementation system. They included the requirements to maintain records of distributing and dispensing, maintaining a noncompliance plan, ensuring patients and HCPs can enroll via fax or online, and that pharmacies can verify authorization online or via phone. We also agreed with the Applicant upon an appropriate timeline for Patient Status Form submission (3 days after the end of the week the ECHO is due). DRM provided feedback regarding adding the information that the REMS will contact stakeholders within 1 business day when they are enrolled in the Camzyos REMS and a requirement to audit pharmacies and wholesalers-distributors no later than 180 days after becoming certified and annually thereafter.*

7.1.4. Timetable for Submission of Assessments

The Applicant proposed submitting REMS assessments (b) (4) and 12 months post approval of the REMS, then annually thereafter.

Reviewer's Comments: *DMAMES and DRM have aligned to require Camzyos REMS assessments to be submitted beginning at 12 months post approval, then annually thereafter. At (b) (4) from approval in other REMS programs, there has historically been minimal data to assess and insufficient time for the Applicant to incorporate any recommendations made by the Agency between the (b) (4) and 12-month assessment reports. In addition, the Agency will be monitoring cases as they are submitted to the FDA Adverse Event Reporting System (FAERS).*

7.1.5. Rems Materials and Key Risk Messages

The Applicant included the following materials in the original REMS proposal:

- (b) (4) Enrollment Form (revised to: Healthcare Provider Enrollment Form): serves to enroll the healthcare provider who prescribes in the REMS and for the HCP to attest they understand the requirements of the REMS as part of the process to become certified to prescribe Camzyos.

- Patient Enrollment Form: completed by the HCP and the patient to enroll the patient into the REMS and requires patients to attest they understand the risks of Camzyos as well as the requirements of the REMS.
- Pharmacy Enrollment Form: completed by the pharmacy's authorized representative on behalf of the pharmacy to enroll and certify into the REMS.
- (b) (4) (revised to Education Program for Healthcare Providers and Pharmacies): serves to inform prescriber and pharmacy authorized representative of the serious risk associated with Camzyos, the REMS requirements, and the responsibilities of healthcare providers and certified pharmacies.
- Program Overview: serves as a quick guide to stakeholder responsibilities in the REMS.
- Healthcare Provider Knowledge Assessment: ensures HCPs understand the risks of Camzyos and the requirements of the REMS prior to becoming certified.
- Patient Brochure (b) (4) (revised to Patient Brochure): serves to inform patients on the serious risk associated with Camzyos therapy as well as the REMS Program and its requirements.
- Patient Status Form: documents ECHO monitoring, drug interaction screening, and authorization to fill a prescription for Camzyos.
- REMS Website: serves a source of information for stakeholders. It allows HCPs, pharmacies, and patients to enroll and certify in the REMS. Healthcare providers will be able to complete and submit the *Knowledge Assessment* and *Patient Status Forms*. Pharmacies will be able to complete and submit the *Knowledge Assessment*, and *Drug Interaction and Counseling Checklist*, and obtain authorization to dispense online. The REMS appended materials, including a link to the Prescribing Information and Medication Guide, will be available and able to be downloaded.

Reviewer's Comments: *We agree with the Applicant's proposed REMS materials, and communicated on September 16, 2021, March 2, 2022, March 9, 2022, April 8, 2022, April 11, 2022, April 13, 2022, and April 21, 2022, April 25, 2022, and April 27, 2022, that changes needed to be made to the proposed materials and new materials should be added to support the REMS requirements. The following additional REMS materials were developed by the Applicant:*

- Pharmacy Authorized Representative Knowledge Assessment: ensures pharmacy authorized representatives understand the risks of Camzyos and the REMS requirements prior to becoming certified.
- Drug Interaction and Counseling Checklist for Pharmacies: documents that the pharmacist has reviewed the patient's medication list, screened for drug interactions, and contacted the HCP if the dose of Camzyos needed to be changed or if the interacting medication needed to be discontinued, and reviewed the Patient Status Form information.

(b) (4) See Section 8 of this review for DRM's proposed Key Risk Messages.

7.1.6. Supporting Document

The REMS Supporting Document includes the background and the Applicant's rationale for the REMS currently under review. The Supporting Document also contains information on stakeholders' responsibility in the REMS, how they carry out those responsibilities, and how the REMS will be implemented. The Applicant appended the *Healthcare Provider Designee Enrollment Form* and the

Healthcare Provider, Healthcare Provider Designee, and Pharmacy Portal screenshots to the supporting document.

Reviewer's Comments: *We acknowledge that in clinical practice, many HCPs may be involved in the patient's care. To decrease burden to prescribers, the Agency agreed with the Applicant's proposal to allow certified prescribers to name a designee to perform certain REMS activities on their behalf. Designees may counsel patients and complete and submit Patient Enrollment Forms and Patient Status Forms.* (b) (4)

We agreed that licensed HCP's including nurse practitioners (NP), registered nurses (RN), physician assistants (PA), and pharmacists (PharmD/RPh) working in the certified HCP's practice may become Designees. Designees are not required to certify in the REMS, but should review the prescribing information, Program Overview, and Education for Healthcare Providers and Pharmacy Authorized Representatives and attest that they have done so using a Designee Enrollment Form. The Designee Enrollment Form is appended to the Camzyos REMS Supporting Document, but designees will need their own log-in to complete the Patient Enrollment Form online.

DRM has requested edits to the Supporting Document on September 16, 2021, March 2, 2021, March 9, 2022, April 8, 2022, April 11, 2022, April 13, 2022, April 21, 2022, and April 25, 2022, including updates to align sections of the Supporting Document with REMS Document and stakeholder attestations. The Applicant included further details in stakeholder requirements, such as addressing how dispensing pharmacists obtain authorization to dispense Camzyos and requesting timetables for contacting healthcare providers about due dates of Patient Status Forms.

7.1.7. Assessment Plan

The Applicant initially submitted a REMS Assessment Plan on January 28, 2021, as part of the Camzyos REMS Supporting Document. This initial Assessment Plan did not capture all metrics necessary to ensure the goal and objectives of the Camzyos REMS were being met. The Applicant was sent revisions to the Assessment Plan by DMAMES on March 9, 2022, and resubmitted the Assessment Plan on March 22, 2022. Minor edits were required, and DMAMES sent the revisions to the Applicant on April 8, 2022. The Assessment Plan was resubmitted by the Applicant on April 18, 2022, April 25, 2022, and April 26, 2022.

A general synopsis of the assessment plan metrics and rationale for metrics is provided below. The REMS Assessment Plan is included in Appendix 10.1 of this review.

Program Outreach and Communication

- **REMS Website**

The Camzyos REMS assessment plan includes metrics to determine that the REMS Website is established and maintained for stakeholders as required in the REMS document.

Program Implementation and Operations

- **Call Center Reports**

The Camzyos REMS assessment plan includes metrics to determine that the REMS Call Center is established and maintained through the life cycle of the program, as required in the REMS document. In addition, with each assessment, types of calls by stakeholder type is obtained to assess unanticipated burden and potential access issues.

- **Program Implementation**

The Camzyos REMS assessment plan includes metrics for the dates the REMS call center was established and fully functional and that stakeholders could be certified in the REMS. These metrics provide context for assessing when the REMS was active and that the requirements in the REMS document were met.

- **REMS Certification and Enrollment**

- Healthcare Providers**

The Camzyos REMS assessment plan includes metrics on healthcare provider certification. The Camzyos REMS requirement for healthcare provider certification supports the objectives *that monitoring for detection of heart failure due to systolic dysfunction with periodic echocardiograms and that screening for drug interactions prior to each dispense* occurs. Certification ensures that healthcare providers attest to being aware of the REMS requirements and the goal of the Mavacamten REMS when they complete the Mavacamten REMS Healthcare Provider Enrollment Form. Certification also requires that the potential healthcare providers who want to prescribe complete a knowledge assessment. The metrics related to healthcare provider certification provide context for the use of Mavacamten and might allow the review team to assess if healthcare providers have difficulties with the certification process. The metrics for completed healthcare provider certification also provide important context when assessing noncompliance with healthcare provider certification.

- Pharmacies**

The Camzyos REMS assessment plan includes metrics on pharmacy certification. The Camzyos REMS requirement that pharmacies are certified helps ensure that the objectives *that monitoring for detection of heart failure due to systolic dysfunction with periodic echocardiograms and that screening for drug interactions prior to each dispense* occurs. Pharmacy Authorized Representatives (AR) attest to being aware of the REMS requirements which includes the requirement not to dispense Mavacamten without receiving authorization from the REMS program. Certification also requires that the prior to certification of the pharmacy, pharmacy ARs complete a knowledge assessment. The metrics associated with pharmacy certification provide context for the use of Mavacamten and may provide information to assess unanticipated burden or issues with patient access. The metrics for completed pharmacy certification also provide important context when assessing noncompliance with pharmacy certification.

- Patients**

The Camzyos REMS assessment plan includes metrics on patient enrollment. The Camzyos REMS requirement for patient enrollment supports the objectives *of the need for monitoring for detection of heart failure due to systolic dysfunction with periodic echocardiograms and for screening for drug interactions prior to each dispense*. Enrolled patients confirm being aware of the REMS requirements and the goals of the Mavacamten REMS when they complete the Mavacamten REMS Patient Enrollment Form. The metrics related to patient enrollment provide context for the use of Mavacamten and may provide information to assess unanticipated burden or issues with patient access. The collection of gender and age was included to provide additional information on the population since teratogenicity is

included in labelling. The team recognizes that this is not an objective of the REMS however it was felt that age and gender might provide important context to understanding the use of the product and support future benefit risk assessments related to the REMS.

Wholesalers-distributors

The Camzyos REMS assessment plan collects metrics on wholesaler-distributors who are authorized to distribute Camzyos. These metrics are collected to provide context for the program including noncompliance and audit information.

- **Noncompliance**

To support the REMS assessment, the Applicant is required to submit noncompliance and audit plans with each REMS assessment.

Noncompliance metrics

The Camzyos REMS assessment plan includes metrics to determine whether dispensing is limited to enrolled patients, based on prescriptions written by certified prescribers, and dispensed by certified pharmacies. These elements to assure safe use (ETASU), are REMS requirements that the Camzyos REMS team has determined are necessary to ensure the benefit of Camzyos outweighs the risk of heart failure due to systolic dysfunction. Enrolled patients and certified prescribers are informed of the REMS requirements and have attested that they will comply with the requirements to monitor for detection of heart failure due to systolic dysfunction with periodic echocardiograms. Certified prescribers and pharmacy authorized representatives attest that they will screen for drug interactions prior to each dispense. The Camzyos REMS has processes in place to restrict dispensing based on stakeholder certification and/or enrollment. Due to these restrictions, a success rate or threshold of 99.9% for each requirement was agreed to by the Agency and Applicant during the REMS development (see March 9, 2022, comments to the Applicant and Applicant March 21, 2022, REMS submission). This threshold aligns with what is achieved in other stable REMS programs as well as what the Institute for Healthcare Improvement suggests would be achieved for a program that utilizes restrictions and is not dependent on reminders and encouragement to achieve its results when stable.²⁸ The Applicant's non-compliance plan will be submitted with each REMS assessment.

Audits

The Camzyos REMS document requires the Applicant to: *maintain adequate records to demonstrate that the REMS requirements have been met including... including records of certified pharmacies and wholesaler-distributors.* The Applicant's supporting document identifies that the Applicant "will audit pharmacies no later than 180 calendar days after they become certified and annually thereafter to ensure that all REMS processes and procedures are in place, functioning, and support the Camzyos REMS". The metrics to determine that these requirements are met are collected in the assessment plan. The Applicant's audit plan will be submitted with each REMS assessment.

- **Utilization Data**

The Camzyos REMS Assessment Plan includes metrics on the number of prescriptions dispensed (authorized) as well as the number of prescriptions denied (not authorized). These metrics provide context for the use of Camzyos and also may allow the review team to assess for evidence of unanticipated burden and problems with access. Prescriptions that are not authorized may act as measures to assess the degree of burden and if the REMS impacts access by causing a delay in obtaining

Camzyos for patients that are eligible to continue therapy. Denials associated with missing echocardiogram and incomplete assessment of drug-drug interactions also support that the REMS is ensuring that the objectives of the REMS are being met and may support impact of the REMS on safety.

Safe Use Behavior

- **Patient Status Forms**

The first objective of the Camzyos REMS is to: *Monitor for detection of heart failure due to systolic dysfunction with periodic echocardiograms*. The Camzyos REMS is designed to accomplish this by restricting dispensing to patients who have had a Camzyos Patient Status Form submitted at the time that echocardiograms are required as described in the Prescribing Information. The metrics collected related to the Camzyos Patient Status Form identify whether the Camzyos Patient Status Forms are complete, the prescriber authorized treatment, as well as other variables that provide context and a potential measure of burden (patients whose echocardiograms were completed off drug as a result of a pre-dispense authorization denial and potential reasons for this). The Applicant and the Agency have agreed that the *Number of first patient shipments sent prior to receipt of a Patient Enrollment Form (numerator) divided by all patients who were dispensed Camzyos (denominator)* will have a compliance rate of 99.9%.

- **Drug Interaction and Counseling Checklist for Pharmacies**

The second objective of the Camzyos REMS is to: *Screen for drug interactions prior to each dispense*. The REMS is designed to accomplish this by restricting distribution to patients who have had drug interactions evaluated by the prescriber and documented on the Patient Status Form and by review of drugs and counseling provided by the pharmacy prior to submitting the Drug Interaction and Counseling Checklist (DICC) to the REMS program and receiving authorization to dispense. The metrics collected identify that the DICC is complete, the pharmacy has documented the presence of any medications that are contraindicated or require dose adjustment and that actions based on these results were taken and align with the recommendations in labelling. The Applicant and the Agency have agreed that the *Number of unique patients who had a Drug Interaction and Counseling Checklist completed prior to their initial dispensing of Camzyos (numerator) divided by the number of patients who initiated therapy with Camzyos (denominator)* will have a compliance rate of 99.9%.

- **Knowledge Assessment**

The Knowledge Assessment for the Camzyos REMS is linked to prescriber certification and pharmacy authorized representative certification. The knowledge assessment consists of ten questions for potential prescribers and ten questions for pharmacy ARs that identify key requirements of the Mavacamten REMS. Both groups of stakeholders are required to successfully complete Knowledge Assessments prior to being certified in the REMS program. The number of completed Knowledge Assessments, method of completion and number of attempts to complete the respective Knowledge Assessments are collected. Additional metrics associated with these requirements are collected to identify any questions in the Knowledge Assessment that require further evaluation related to the adequacy of the knowledge assessment questions and the Camzyos (mavacamten) REMS Education Program for Healthcare Providers and Pharmacies.

- **Key Performance Indicator**

The Key Performance Indication (KPI) is the measure which is essential in determining the success of the Camzyos REMS program and ensures that the REMS is functioning as designed. Following internal discussion with DMAMES, Division of Risk Management and the Applicant and initially presented to the REMS Oversight Committee on August 21, 2022, as well as communications with the Applicant (March 9, 2022, comments to the Applicant and Applicant March 21, 2022, REMS submission) the following KPI and threshold for success was identified.

The KPI is the number of prescriptions dispensed with an authorization from the REMS program when the prescription:

- i. Will be dispensed from a certified pharmacy
- ii. Is written by a certified healthcare provider
- iii. Is written for an enrolled patient
- iv. Has a completed Patient Status form that documents an appropriately timed echocardiogram
- v. Has a completed Drug Interaction and Counseling Checklist for Pharmacies that documents appropriate actions were taken prior to authorization

The threshold for the KPI is that 99.9% of dispenses are associated with an approved authorization.²⁹

Reviewer's Comments: *DMAMES and DRM agree that the Assessment Plan submitted on April 18, 2022, is acceptable and captures all necessary metrics.*

7.1.8. Summary of OPDP Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on February 18, 2022, and completed a consult review on April 7, 2022, by Charuni Shah.³⁰ DRM accepted most recommendations and provided them in comments to the Applicant on April 18, 2022. These included editing the titles of slides to mirror the content. OPDP had concerns regarding some risk messaging language about the severity of heart failure that the Medication Guide contained, but the Medication Guide no longer contains this language.

7.2. Other Proposed Risk Management Activities

The Applicant proposed a Camzyos Pregnancy Surveillance Program based on a prospectively and proactively collected cohort of pregnant women diagnosed with HCM and exposed to Camzyos.

Reviewer's Comments: *We note that these other activities proposed by the Applicant are outside of the scope of the REMS program and defer to the Division of Pediatric and Maternal Health for review and input.*

8. Discussion of Need for a REMS

In the ongoing clinical review, the Clinical Reviewer recommends approval of mavacamten on the basis of the efficacy and safety information currently available.

Results from the clinical trials demonstrated Camzyos was superior to placebo in improving both functional capacity and symptom burden in patients with oHCM. The major safety concern of heart

failure due to systolic dysfunction is a result of excessive pharmacologic effect and may be serious and potentially lethal. In the clinical trials, both PK (drug level) and PD (ECHO) monitoring were employed to monitor patients for this risk, and subjects experienced heart failure due to systolic dysfunction at plasma concentrations thought to be safe from a PK standpoint and while subjects had been taking Camzyos for an extended period of time. Subjects in the clinical trials experienced significant decreases in LVEF with complications including hospitalization for multi-system organ failure. In the pivotal clinical trial, approximately half of patients who experienced LVEF <50% were asymptomatic.³¹

As the assumed prescribing population are cardiologists, it is expected they possess the skills and knowledge to identify and manage heart failure, however, they must be aware that their patient's left ventricular function is deteriorating dangerously so that they take appropriate action. There were reports in the clinical trial of ECHOs being misread that lead to improper dose increases, which in turn caused patients to experience heart failure.³¹ We expect that the risk of heart failure may be higher in the postmarketing setting when compared to a tightly controlled clinical trial setting. In the postmarket setting, it is possible that healthcare providers may not be aware of the risk and need for and frequency of ECHO monitoring required to safely prescribe Camzyos. Patients may miss ECHOs required at baseline and at periodic intervals, and therefore may receive Camzyos without the monitoring required for the safe use of the drug. Based on these observations, the review team recommends PD monitoring with routine ECHOs is necessary to ensure the benefits outweigh the risks.

The review team carefully weighed the burden on stakeholders with the benefit-risk profile of Camzyos to determine the appropriate risk management strategy. DRM and DCN agree that a REMS with ETASU is necessary to ensure the benefits of Camzyos outweigh the risk of heart failure due to systolic dysfunction.

The Camzyos REMS was discussed at the REMS Oversight Committee (ROC)^g on August 4th, 2021. The clinical and REMS review teams proposed a REMS with ETASU for Camzyos to ensure the benefits outweigh the risk of heart failure due to systolic dysfunction (symptomatic left ventricular ejection fraction (LVEF) < 50%) resulting from excessive pharmacologic effect of Camzyos. The proposed REMS would require periodic echocardiographic assessment of LVEF to detect mavacamten-induced depression of ventricular dysfunction early and prevent further deterioration through drug discontinuation or dose adjustment. The ROC concurred with the review team but had concerns regarding drug-drug interactions (DDIs) and the unknown effect of metabolizer status on the potential of adverse events.³²

After OCP's analysis of the Applicant's modeling by CYP2C19 genotype, a Discipline Review Letter issued on September 30, 2021 noted that prospective CYP2C19 genotyping and availability of a companion diagnostic may be required to use Camzyos and manage risks for patients who are poor CYP2C19

^g As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

metabolizers.⁹ OCP also expressed concerns regarding the challenges in therapeutic management of Camzyos including an inherent risk from inadvertent drug-drug interactions, including those with over-the-counter products, that are difficult to control in clinical use. DCN worked with OCP on determining adequate posology and dosing instructions for poor metabolizers and drug-drug interactions (DDIs). Multiple discussions between the review team and the Applicant followed, many of which centered around the need for and feasibility of developing a companion diagnostic to prospectively genotype all patients prior to beginning mavacamten therapy. Team members from the Center for Devices and Radiological Health (CDRH) noted that there are no CYP2C19 genotype diagnostics on the market for the purpose of ensuring the safe use of a product, and the Applicant would need to develop a companion diagnostic for mavacamten prior to approval if prospective genotyping is required for safe use of the product. Given that the time required for the Applicant to develop a companion diagnostic would lead to a multi-year delay for patients as well as consideration of the low prevalence of poor CYP2C19 metabolizer phenotype (1-5% of the US population), DCN worked with OCP to seek other options that do not require prospective genotyping.

The dosing algorithm and monitoring schedule detailed in Section 5.3 of the Camzyos label allows for the safe and effective use of Camzyos by patients regardless of metabolizer status. However, safety concerns lingered regarding DDIs, especially those involving nonprescription medications and supplements that are moderate or strong inhibitors of CYP2C19 or a strong inhibitor of CYP3A4. OCP recommended either to avoid concomitant administration of Camzyos with the interacting drugs or dose reduction of Camzyos based on the expected magnitude of effect. Camzyos labeling will convey that concomitant administration of Camzyos with a moderate or strong inhibitor of CYP2C19 as well as a strong inhibitor of CYP3A4 are contraindicated. Due to the number of interacting drugs, particularly those available over the counter and the magnitude of pharmacological effect, OCP recommendations were to decrease the dose of Camzyos one level (i.e., 10 mg to 5 mg) and to complete ECHO monitoring at Week 4, Week 12, and every 12 weeks thereafter with concomitant administration of Camzyos with a weak inhibitor of CYP2C19 or moderate inhibitor of CYP3A4.²⁵

To further mitigate the risk of heart failure due to systolic dysfunction because of drug-drug interactions, DRM added screening for DDIs prior to each dispense as a second objective to the proposed Camzyos REMS. DCN and DRM discussed multiple options to mitigate the risk of DDIs contributing to heart failure due to systolic dysfunction and concluded that screening for DDIs should be done by the healthcare provider or their designee prior to treatment initiation and with each clinical visit, i.e., with every *Patient Status Form* completion. Additionally, the pharmacist should also screen for DDIs prior to each dispense to include any medications that may have been recently added or purchased between visits. To accomplish this objective, DRM added a *Drug Interaction and* (b) (4) *Counseling Checklist for Pharmacies* as a REMS material to ensure patients' prescription and over the counter medications and supplements are reviewed by the certified pharmacy for drug-drug interactions prior to each dispense to decrease the probability of drug-drug interactions. The data collected in the *Patient Status Form* and *Drug Interaction and* (b) (4) *Counseling Checklist for Pharmacies* also serves as decision support for the pharmacy staff when filling prescriptions for Camzyos. The REMS Oversight Committee was updated via email with the new information regarding the rationale to screen for drug

interactions prior to dispensing Camzyos, and the strategy to screen both at the healthcare provider clinic visit as well as documenting a final drug interaction screening at dispense.³³

The minimum necessary REMS elements required include:

1. Prescriber Certification (ETASU A) to ensure prescribers are educated about the risks, the need to enroll and counsel patients, and the need to monitor patients
2. Pharmacy Certification (ETASU B) to ensure that prescribers are certified, patients are enrolled and authorized to receive the drug prior to dispensing as well as to screen for DDI's and appropriate dosing of Camzyos
3. Safe Use Conditions (ETASU D) to ensure that Camzyos is dispensed to patients who have been enrolled in the REMS, who have received counseling from the prescriber about the risks and monitoring requirements and who have completed the monitoring requirements
4. Patient Monitoring (ETASU E) to ensure prescribers attest and document that they have completed monitoring of the patient's cardiac function at baseline and periodically as described in the Prescribing Information and have assessed the appropriateness of initiating treatment, and during ongoing therapy, the appropriateness of continuing treatment. ETASU E also ensures prescribers and pharmacies screen for DDI's and make appropriate dose changes.

DRM concludes that based on the review of the proposed REMS received on April 27, 2022, the REMS will support actions that will mitigate the risks of heart failure due to systolic dysfunction associated with Camzyos. The REMS will ensure that patients are getting Camzyos in the safest manor and supports healthcare providers with appropriate dosing and monitoring.

8.1 REMS Materials and Key Risk Messages

Although not part of the overall goal of the REMS, education of stakeholders is used as a tool to achieve the REMS goals. The following REMS materials will provide education and support the risk messaging of the REMS:

- Healthcare Provider Enrollment Form
- Patient Enrollment Form
- Pharmacy Enrollment Form
- Education Program for Healthcare Providers and Pharmacies
- Program Overview
- Healthcare Provider Knowledge Assessment
- Pharmacy Authorized Representative Knowledge Assessment
- Patient Brochure
- Patient Status Form
- Drug Interaction and Counseling Checklist for Pharmacies
- REMS Website

Key Risk Messages for Healthcare Providers

- Camzyos can cause heart failure due to systolic dysfunction (LVEF < 50%)
- Healthcare Providers must perform ECHO monitoring before treatment and periodically during treatment as described in the prescribing information

- Healthcare Providers must assess the patient's prescription and non-prescription medications and supplements for DDI's

Key Risk Messages for Patients

- Camzyos can cause heart failure (when your heart is unable to pump enough blood to the body)
- You will need to have regular echocardiograms to check your heart while taking Camzyos
- Your healthcare provider and pharmacist will go over your current prescription and over the counter medications and supplements to check for any that interact with mavacamten
- You must inform your healthcare provider of all medicines you take and any changes in medicines, including over-the-counter and supplements
- You must inform your healthcare prescriber of any new or worsening symptoms of heart failure

Key Risk Messages for Pharmacies

- Camzyos can cause heart failure due to systolic dysfunction (LVEF <50%)
- Healthcare providers must perform ECHO monitoring at baseline and periodically during treatment as describing in the Prescribing Information. This must be documented on the *Patient Status Form* and submitted to the REMS
- Pharmacists must assess the patient's prescription and nonprescription medications and supplements for DDIs, and submit the results and DDI resolutions to the REMS using the *Drug Interaction and Counseling Checklist for Pharmacies*
- No more than a 35-day supply of Camzyos may be dispensed
- Prior to dispensing, the pharmacist must ensure the prescriber is certified, the patient is enrolled, the healthcare provider has authorized the patient to receive Camzyos, the patient is counseled, and the pharmacy has identified and resolved any DDIs

9 Conclusion & Recommendations

The risk of heart failure due to systolic dysfunction associated with Camzyos is serious and potentially lethal, and it is necessary for HCPs, pharmacies that dispense Camzyos, and patients to understand this risk and the necessary monitoring and drug interactions. Based on the magnitude and severity of the risk of heart failure due to systolic dysfunction, DRM and DCN agree that a REMS consisting of prescriber certification, pharmacy certification, safe use conditions – patient enrollment, and monitoring of patients while taking Camzyos is necessary to ensure that the benefits outweigh the risk. The REMS will also include an implementation system and timetable for submission of assessments.

DRM finds the Applicant's Proposed REMS received on April 27, 2022, to be acceptable and is appended to this review.

10 Appendices

10.1 Camzyos REMS Assessment Plan

The Camzyos REMS Assessment Plan must include, but is not limited to, the following:

Program Outreach and Communication (provide data at the 1-year assessment only)

1. REMS Program Website
 - a) Date REMS website went live
 - b) Number of total visits and unique visits to the REMS Program Website
 - c) Number and type of Camzyos REMS materials downloaded or accessed

Program Implementation and Operations

2. REMS Call Center Reports (provide data for two previous reporting periods, the current reporting period, and cumulatively)
 - a) Number of calls by stakeholder type (patient, healthcare provider, designee, pharmacy, wholesalers-distributors, other)
 - b) Summary of reasons for calls (e.g., enrollment question) and stakeholder type (patients, healthcare provider, designee, pharmacy, other). Limit the summary to the top five reasons for calls by each stakeholder group.
 - c) If the summary reason for the call(s) indicates a complaint, include details on the nature of the complaint(s) and whether the caller indicated potential REMS burden or patient access issues
 - d) If the summary reason for the call(s) indicates an adverse event related to heart failure or a contraindicated drug or drug interaction, include details and the outcome of the call(s)
 - e) Percentage of calls to the REMS Call Center that were answered within 20 minutes.
 - f) The shortest wait time for a call to be answered, the longest wait time for a call to be answered and the median time for a call to be answered
 - g) Percentage of calls to the REMS Call Center where the caller abandoned the call before the call was answered
 - h) The shortest wait time at which a call was abandoned, the longest wait time before the call was abandoned and the median wait time for a call to be abandoned
3. Program Implementation (provide data at the 1-year assessment only)
 - a) Date of first commercial availability of Camzyos
 - b) For each stakeholder (healthcare providers, designees, pharmacies, patients), the date when they could become certified
 - c) Date when the Camzyos REMS Call Center was established and fully operational
4. REMS Certification and Enrollment (provide data for two previous reporting periods, the current reporting period and cumulatively)
 - a) Healthcare Providers
 - i. Number of newly certified healthcare providers and number of active (i.e., who have prescribed at least once during the reporting period) healthcare providers stratified by credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other), specialty (e.g., Cardiology, Electrophysiology, Geneticist, Other), and geographic region (defined by US Census). If "Other" accounts for >10% of respondents, provide the most common specialties identified. Specifically identify and categorize if a specialty is within cardiology or non-cardiology.
 - b) Number of Designees stratified by role (e.g., RPh/PharmD, RN, NP, or PA).
 - i. Method of healthcare provider and designee certification (online or fax).
 - c) Pharmacies
 - i. Number of newly certified pharmacies

- ii. Number of active pharmacies (i.e., have dispensed Camzyos)
 - d) Patients
 - i. Number of newly enrolled patients and number of active (i.e., received at least one dispense of Camzyos) patients stratified by a combined variable of age and gender and geographic region. Provide the minimum and maximum age of enrolled patients. For gender/age variable use age ranges of less than 18, 18-40, 41-60, 61 and older
 - e) Wholesalers-distributors
 - i. Number of newly contracted wholesalers-distributors and number of active (i.e., have shipped Camzyos) wholesalers-distributors.
5. REMS Compliance (provide data for two previous reporting periods, the current reporting period, and cumulatively)
- a) A copy of the non-compliance plan, including the criteria for non-compliance for healthcare providers, pharmacies, and wholesalers-distributors, actions taken to address noncompliance for each case, and which event lead to decertification from the Camzyos REMS (Beginning with the 1-year assessment and annually thereafter)
 - b) Audits
 - i. A copy of the audit plan for pharmacies and wholesalers/distributors
 - ii. Report of audit findings for each stakeholder (pharmacies and wholesalers-distributors)
 - iii. Number of audits expected, and the number of audits performed.
 - iv. Documentation of completion of training for relevant staff.
 - v. Documentation of processes and procedures in place for complying with the Camzyos REMS.
 - vi. Verification for each audited stakeholder's site that the designated Authorized Representative remains the same. If different, document that the pharmacy has re-certified with the name and contact information for the new Authorized Representative.
 - vii. Number and types of deficiencies noted for each group of audited stakeholders as a percentage of audited stakeholders.
 - viii. For each Audited Pharmacy, number of the following deficiencies (numerator) divided by the number of dispenses audited at that pharmacy (denominator):
 - 1. Healthcare provider not certified, and prescription dispensed
 - 2. Patient not enrolled and prescription dispensed
 - 3. Drug Interaction and Counseling Checklist not completed, and prescription dispensed
 - 4. Audit of Drug Interaction and Counseling Checklist forms that identified a drug was dispensed but a required action not taken
 - 5. Authorization denied and prescription dispensed
 - ix. For stakeholders with deficiencies noted, the number that successfully completed a Corrective and Preventative Action (CAPA) plan and as a percentage of those for which a CAPA plan was requested.
 - x. For any stakeholders who did not complete the CAPA Plan, a description of actions taken.
 - c) Healthcare provider noncompliance (For each non-compliance event, the source of the

- report, a description of the event, the root cause analysis of the event, and corrective actions taken)
- i. Number of healthcare providers who were non-compliant with the Camzyos REMS program requirements. Provide as a percentage of active healthcare providers.
 - ii. Number of healthcare providers who were de-certified and reasons for de-certification also provide as a percentage of active healthcare providers. Include if any healthcare providers were re certified.
- d) Pharmacies (For each non-compliance event, the source of the report, a description of the event, the root cause analysis, and corrective actions taken)
- i. Number of pharmacies for which non-compliance with the Camzyos REMS is detected (numerator) divided by all pharmacies dispensing Camzyos (denominator)
 - ii. The number of non-certified pharmacies that dispensed Camzyos (numerator) divided by all pharmacies that dispensed Camzyos (denominator). A compliance rate of 99.9% is expected.
 - iii. Number of Camzyos prescriptions dispensed by non-certified pharmacies (numerator) divided by all prescriptions Camzyos dispensed (denominator) and the actions taken to prevent future occurrences. A compliance rate of 99.9% is expected.
 - iv. Number of Camzyos prescriptions dispensed that were written by non-certified healthcare providers (numerator) divided by all dispensed prescriptions (denominator). For prescriptions dispensed that were written by non-certified healthcare providers, provide the root cause analysis and the actions taken to prevent future occurrences. A compliance rate of 99.9% is expected.
 - v. Number of Camzyos prescriptions dispensed to non-enrolled patients (numerator) divided by all dispensed prescriptions (denominator). For prescriptions dispense to non-enrolled patients provide a root cause analysis and the actions taken to prevent future occurrences. A compliance rate of 99.9% is expected.
 - vi. Number of Camzyos prescriptions dispensed to non-enrolled patients based on a prescription from a non-certified healthcare provider (numerator) divided by all dispensed prescriptions (denominator). For prescriptions dispensed to non-enrolled patients based on a prescription from a non-certified healthcare provider provide a root cause analysis and the actions taken to prevent future occurrences. A compliance rate of 99.9% is expected.
 - vii. Number of times a Camzyos prescription was dispensed because a certified pharmacy bypassed the Camzyos REMS authorization processes (numerator) divided by all certified pharmacies (denominator). Provide a root cause analysis and including a description of how the events were identified and any corrective actions taken. A compliance rate of 99.9% is expected.
 - viii. Number of pharmacies decertified, reasons for decertification, and actions to address non-compliance. Provide as a ratio the number of pharmacies decertified (numerator) divided by all certified pharmacies (denominator)
- e) Wholesalers-distributors (For each non-compliance event, the source of the report, a description of the event, the root cause analysis, and corrective actions taken)
- i. Number of contracted wholesalers-distributors for which non-compliance with the Camzyos REMS is detected (numerator) divided by the number of contracted wholesalers-distributors (denominator)

- ii. Number of wholesalers-distributors suspended from distributing, reasons for the suspension, and actions to address non-compliance
 - iii. Number of times Camzyos was distributed to a non-certified pharmacy (numerator) divided by the number of distributions of Camzyos (denominator)
- 6. Utilization Data (provide data for two previous reporting periods, the current reporting period, and cumulatively)
 - a) Number of prescriptions (new and refills) dispensed, stratified by:
 - i. Healthcare provider degree/credentials and geographic region
 - ii. Patient demographics (age and gender, and geographic region)
 - b) The number of prescriptions received and denied (not authorized), stratified by:
 - i. Reasons and number of denials (numerator) divided by all denials (denominator)
 - 1. Healthcare provider not certified
 - 2. Prescription written by designee.
 - 3. Patient not enrolled
 - 4. Patient status form documenting echocardiogram not submitted on appropriate schedule
 - 5. Drug Interaction and Counseling Checklist-not completed
 - 6. Drug interaction or contraindicated drug identified, and appropriate actions not taken
 - 7. Other reasons for denial not categorized above
 - ii. Healthcare provider degree/credentials and geographic region
 - c) Number of unique healthcare providers who wrote prescriptions dispensed in the reporting period (active healthcare providers)
 - d) Number of unique patients receiving Camzyos, stratified by age, gender, and geographic region
- 7. Burden to the Healthcare System and/or Barriers to Patient Access
 - a) Reports to the Camzyos REMS Call Center indicating a burden to the healthcare system or barriers to patient access. Assessment of whether burden is attributable to the REMS, insurance, health care availability, other

Safe Use Behavior

- 8. Patient Status Forms (provide data for two previous reporting periods, current reporting period and cumulatively)
 - a) Number of Patient Status Forms expected, received, and outstanding as of the REMS assessment cut-off date
 - b) Number of first patient shipments sent prior to receipt of a Patient Enrollment Form (numerator) divided by all patients who were dispensed Camzyos (denominator). A compliance rate of 99.9% is expected.
 - c) Number of unique patients who had a Patient Status Form submitted who the healthcare provider confirmed reviewing the echocardiogram for (numerator) divided by number of unique patients who had a Patient Status Form submitted (denominator)
 - d) Number of unique patients who had a Patient Status Form submitted who the healthcare provider authorized treatment for (numerator) divided by number of unique patients who had a patient status form submitted (denominator)
 - e) Number of Patient Status Forms outstanding from previous reporting periods that were completed in the current reporting period (numerator) divided by the number of

- outstanding Patients Status Forms from the previous reporting period (if applicable)
 - f) Number of patients whose echocardiogram was completed off drug as a result of an authorization denial and reason (e.g., drug not dispensed due to missing Patient Status Form, insurance issues prevented drug dispensing, transportation issues prevented patient from obtaining echocardiograms)
 - g) Number of Patient Status Forms on which the healthcare provider indicated that the patient experienced a clinical heart failure event requiring hospitalization
 - i. Number of Patient Status Forms on which the healthcare provider indicated the patient experienced a decrease in LVEF to <50%
 - h) Number of patients who were not authorized to receive Camzyos as indicated on the Patient Status Form
- 9. Drug Interaction and Counseling Checklist for Pharmacies (provide data for two previous reporting periods, current reporting period and cumulatively)
 - a) Number of unique patients who had a Drug Interaction and Counseling Checklist completed prior to their initial dispensing of Camzyos (numerator) divided by the number of patients who initiated therapy with Camzyos (denominator). Compliance rate of 99.9%.
 - b) Number of prescriptions dispensed that had a Drug Interaction and Counseling Checklist completed prior to dispensing (numerator) divided by the number of prescriptions dispensed for Camzyos (denominator). A compliance rate of 99.9% is expected.
 - c) Number of Drug Interaction and Counseling Checklist that identified a concurrent contraindicated medicines (numerator) divided by the total number of Drug Interaction and Counseling Checklists completed (denominator)
 - d) For those Drug Interaction and Counseling Checklists that identified a concurrent contraindicated medicines indicate the source of the drug interaction and action taken after healthcare provider was contacted including:
 - i. Source
 - 1. Interacting drug prescribed by Camzyos certified healthcare provider/designee
 - 2. Interacting drug prescribed by other healthcare provider
 - 3. Interacting drug purchased over the counter by patient
 - ii. Action taken
 - 1. Camzyos discontinued
 - 2. Contraindicated drug discontinued
 - e) Number of Drug Interaction and Counseling Checklist that identified a concurrent medicine that required a dosage reduction (numerator) divided by the total number of Drug Interaction and Counseling Checklists completed (denominator).
 - f) For those Drug Interaction and Counseling Checklist that identified a concurrent medicine that required a dosage reduction indicate source of drug interaction and action taken after healthcare provider was contacted including:
 - i. Source
 - 1. Interacting drug prescribed by Camzyos certified healthcare provider/designee
 - 2. Interacting drug prescribed by other healthcare provider
 - 3. Interacting drug purchased over the counter by patient

- ii. Action taken
 - 1. Camzyos discontinued
 - 2. Camzyos dose decreased
 - 3. Other medicine(s) discontinued
 - g) Any information obtained from audits, or self-reported by pharmacies that indicated that a patient did receive a contraindicated medicine, while taking Camzyos expressed by the number of patients who received at least one shipment (dispensing) of Camzyos who were also taking a concurrent contraindicated medicine (numerator) divided by the total number of patients with at least one shipment (dispensing) of Camzyos (denominator)
 - i. For all occurrences, include the contraindicated drug name, dose, and duration of therapy
- 10. Knowledge Assessments (provide data at the 1-year and 2-year assessment reports only)
 - a) Number of completed Healthcare Provider Knowledge Assessments, including the method of completion and number of attempts to complete
 - b) A summary of the most frequently missed Healthcare Provider Knowledge Assessment questions
 - c) A summary of potential comprehension or perception issues identified with the Healthcare Provider Knowledge Assessment
 - d) Number of completed Pharmacy Authorized Representative Knowledge Assessments, including the method of completion and number of attempts to complete
 - e) A summary of the most frequently missed Pharmacy Authorized Representative Knowledge Assessment questions
 - f) A summary of potential comprehension or perception issues identified with the Pharmacy Authorized Representative Knowledge Assessment
- 11. Report on Key Performance Indicator (KPI)
 - a) The KPI is the number of prescriptions dispensed with an authorization from the REMS program when the prescription:
 - i. Will be dispensed from a Certified pharmacy
 - ii. Written by a Certified prescriber
 - iii. Written for an Enrolled patient
 - iv. Has a completed Patient Status form that documents an appropriately timed echocardiogram
 - v. Has a completed Drug Interaction and Counseling Checklist that documents appropriate actions were taken prior to authorization.

The threshold for the KPI is that 99.9% of dispenses are associated with an approved authorization

Overall Assessment of REMS (b) (4)

- 12. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

10.2 References

1. Myokardia Inc., a wholly owned subsidiary of Bristol Myers Squibb, Proposed mavacamten (NDA 241998) Prescribing Information, April 1, 2022.
2. Myokardia, Inc., a wholly-owned subsidiary of Bristol Myers Squibb, Summary of Clinical Efficacy of Mavacamten (NDA 214998), January 28, 2021.
3. Division of Cardiology and Nephrology Clinical and Statistical Integrated Review of Mavacamten (NDA 214998), April 28, 2022.
4. FDA Office of Orphan Products Development, Orphan Drug Designation #15-5150 Letter, April 27, 2016.
5. Proctor, B., FDA Meeting Minutes from the mavacamten (IND 121904) pre-NDA Teleconference on July 12, 2020, DARRTS ID# 4642648.
6. Proctor, B. Mavcamten (IND 121904) Grant Breakthrough Therapy Designation Letter, July 22, 2020.
7. Childers, A. Mid-Cycle Communication for Mavacamten (NDA 214998) July 29, 2021, DARRTS ID # 4833568.
8. Cunningham, C. Division of Risk Management Interim Comments on the Proposed Mavacamten (NDA 214998) REMS, September 16, 2021, DARRTS ID #4857915.
9. Childers, A., Discipline Review Letter for Camzyos (mavacamten) (NDA 214998) DARRTS ID 12355403.
10. Childers, A., Review Extension - Major Amendment Letter for mavacamten (NDA 214998), November, 18, 2021.
11. Cunningham, C., Division of Risk Mangement Interim Comments on the Proposed Mavacamten (NDA 214998) REMS, March 2, 2022, DARRTS ID# 4945947.
12. Jones, Charlotte T., Division of Medication Error Prevention and Analysis Comments on the Proposed Camzyos (mavacamten, NDA 214998) REMS Assessemnt Plan, March 9, 2022, DARRTS ID# 4949989.
13. Cunningham, C., Division of Risk Management Interim Comments on the Proposed Mavacamten (NDA 214998) REMS, March 9, 2022, DARRTS ID# 4949882.
14. Cunningham, C. Division of Risk Mangement Interim Comments on the Proposed Mavacamten (NDA 214998) REMS, April 8, 2022, DARRTS ID# 4966211
15. Cunningham, C. Division of Risk Management Interim Comments on the Camzyos (mavacamten NDA 214998) REMS, April 21, 2022, DARRTS ID#13040834.
16. Mavacamten REMS Oversight Committee Meeting Executive Summary Document August 4, 2021.
17. American Heart Association "Hypertrophic Cardiomyopathy". <https://www.heart.org/en/health-topics/cardiomyopathy/what-is-cardiomyopathy-in-adults/hypertrophic-cardiomyopathy>. Updated November 17, 2020. Accessed June 13, 2021, 2021.
18. Nishimura RA SH, Schaff HV. Hypertrophic Obstructive Cardiomyopathy. *Circulation Research*. 2017;121(7):771-783.
19. Ommen SR MS, Burke MA, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: Executive Summary. *Circulation* 2020;142(25).
20. Mayo Clinic "Hypertrophic Cardiomyopathy, Diagnosis and Treatment". <https://www.mayoclinic.org/diseases-conditions/hypertrophic-cardiomyopathy/diagnosis-treatment/drc-20350204>. Updated June 2, 2020. Accessed August 8, 2021, 2021.
21. Myokardia, Inc., a whollyowned subsidiary of Bristol Myers Squibb, Final Camzyos (mavacamten) Prescribing Information, April 22, 2022.
22. MedWatch Report of Patient (b) (6) on April 6, 2021.

23. Myokardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb. Response to Clinical Pharmacology Information Request Mavacamten (NDA 214998).
24. Myokardia Inc., a wholly owned subsidiary of Bristol Myers Squibb Proposed Camzyos (mavacamten NDA 214998) Label, January 18, 2022 Submisison
25. Bende, G. et al., Office of Clinical Pharmacology Review of Mavacamten (NDA 214998) Amendment, January 28, 2021 DARRTS ID#12355403.
26. MyoKardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb, REMS Correspondence: Proposed REMS Schedule and Dosing Limits, February 4, 2022.
27. Myokardia, a wholly owned subsidiary of Bristol Myers Squibb REMS Correspondence, March 21, 2022.
28. T. Nolan, R. Resar, C. Harden. Improving the Reliability of Health Care. In: *IHI Innovation Series White Paper*. Boston: Institute for Healthcare Improvement; 2004.
29. Jones, C.T. Division of Mitigation Assessment and Medication Error Surveillance Rationale for the Proposed Camzyos REMS Assessment Plan, April 28, 2022, DARTTS ID# 12355403.
30. Shah, C. Office of Prescription Drug Promotion Review of the Proposed Mavacamten (NDA 214998) REMS, April 7, 2022.
31. Myokardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb, Summary of Clinical Safety of Mavacamten (NDA 214998), January 28, 2021.
32. Minutes from the August 4, 2021 Mavacamten REMS Oversight Committee Meeting
33. REMS Oversight Committee Updates on the Mavacamten (NDA 214998) REMS via email February 16, 2022.

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/s/

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Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Application Number	214998
Submission Type/Number	Original-1
OSE RCM #	2021-191
Reviewer Name(s)	Charlotte Jones, MD, PhD, MSPH (DMAMES)
Team Leader	Shelly Harris, ScD, MPH (DMAMES)
Deputy Division Director	Doris Auth, PharmD (DMAMES)
Review Completion Date	April 28, 2022
Subject	Rationale Review for the Camzyos (Mavacamten) Risk Evaluation and Mitigation Strategy (REMS) Assessment Plan
Established Name	Mavacamten
Trade Name	Camzyos
Name of Applicant	Myokardia, Inc. Bristol Myer Squibb
Therapeutic Class	Cardiac myosin inhibitor
Formulation(s)	2.5mg, 5mg, 10mg and 15mg oral capsules
Submission Date	Starting dose of 5mg daily with dosing adjustments as identified in the prescribing information.

1. Introduction

The Camzyos REMS Assessment Plan includes the metrics that the Applicant and Agency intend to use to assess the performance of the REMS. The Assessment plan also includes metrics for assessing the impact of the REMS on the healthcare delivery system burden and balancing measures (unintended consequences/harms) and patient access to the drug.

2. Background

The Camzyos (mavacamten) application was submitted on January 28, 2021, with the proposed indication for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms. The Camzyos REMS is being required in order to ensure that the benefits outweigh the risks of heart failure due to systolic dysfunction.

2.1 REMS Goal and Elements

The goal of the Camzyos risk evaluation and mitigation strategy (REMS) program is to mitigate the risk of heart failure due to systolic dysfunction.

Objectives:

1. Monitor for detection of heart failure due to systolic dysfunction with periodic echocardiograms.
2. Screen for drug interactions prior to each dispense.

The REMS elements include:

Elements to Assure Safe Use

- Healthcare providers who prescribe Camzyos are specially certified
- Pharmacies and healthcare settings that dispense Camzyos are specially certified
- Camzyos is dispensed to patients with evidence or other documentation of safe-use conditions
- Each patient using Camzyos is subject to certain monitoring
- Implementation System
 - The Applicant must provide training to healthcare providers who prescribe Camzyos
 - The Applicant must provide training to pharmacies that dispense Camzyos
 - The Applicant must authorize dispensing based on REMS requirements
 - The Applicant must ensure compliance with the REMS
- The timetable for submission of assessments for the Camzyos (mavacamten) REMS is annually.

3. Materials Reviewed for NDA 214998

- August 4, 2021, REMS Oversight Committee Meeting minutes
- January 25, 2022, REMS Assessment Plan submitted as part of supporting document
- February 16, 2022, ROC Oversight Committee Mavacamten email
- March 1, 2022, Presentation to review team identifying proposed Key Performance Indicators (KPIs) for Mavacamten
- March 2, 2022, DRM-provided comments and redlined REMS materials to the Applicant on the January 25, 2022, REMS submission
- March 9, 2022, DMAMES comment to the Applicant with proposed Assessment Plan including KPIs
- March 21, 2022, NDA REMS submission
- April 18, 2022, NDA REMS submission
- April 26, 2022, NDA REMS submission
- April 27, 2022, NDA REMS submission

4. Summary of the Camzyos (mavacamten) REMS Assessment Plan

A general synopsis of the assessment plan metrics and rationale for metrics is provided below. Not all metrics that provide context or that are collected across all REMS for future research or Agency potential needs are included in this rationale review.

Program Outreach and Communication

4.1 REMS Website

The Camzyos REMS assessment plan includes metrics to determine that the REMS Website is established and maintained for stakeholders as required in the REMS document.

Program Implementation and Operations

4.2 Call Center Reports

The Camzyos REMS assessment plan includes metrics to determine that the REMS Call Center is established and maintained through the life cycle of the program, as required in the REMS document. In addition, with each assessment, types of calls by stakeholder type is obtained to assess unanticipated burden and potential access issues.

4.3 Program Implementation

The Camzyos REMS assessment plan includes metrics for the dates the REMS call center was established and fully functional and that stakeholders could be certified in the REMS. These metrics provide context for assessing when the REMS was active and that the requirements in the REMS document were met.

4.4 REM Certification and Enrollment

4.4.1 Healthcare Providers

The Camzyos REMS assessment plan includes metrics on healthcare provider certification. The Camzyos REMS requirement for healthcare provider certification supports the objectives *that monitoring for detection of heart failure due to systolic dysfunction with periodic echocardiograms and that screening*

for drug interactions prior to each dispense occurs. Certification ensures that healthcare providers attest to being aware of the REMS requirements and the goal of the Mavacamten REMS when they complete the Mavacamten REMS Healthcare Provider Enrollment Form. Certification also requires that the potential healthcare providers who want to prescribe complete a knowledge assessment. The metrics related to healthcare provider certification provide context for the use of Mavacamten and might allow the review team to assess if healthcare providers have difficulties with the certification process. The metrics for completed healthcare provider certification also provide important context when assessing noncompliance with healthcare provider certification.

4.4.2 Pharmacies

The Camzyos REMS assessment plan includes metrics on pharmacy certification. The Camzyos REMS requirement that pharmacies are certified helps ensure that the objectives *that monitoring for detection of heart failure due to systolic dysfunction with periodic echocardiograms and that screening for drug interactions prior to each dispense* occurs. Pharmacy Authorized Representatives (AR) attest to being aware of the REMS requirements which includes the requirement not to dispense Mavacamten without receiving authorization from the REMS program. Certification also requires that the prior to certification of the pharmacy, pharmacy ARs complete a knowledge assessment. The metrics associated with pharmacy certification provide context for the use of Mavacamten and might allow the review team to assess for evidence of unanticipated burden and problems with access. The metrics for completed pharmacy certification also provide important context when assessing noncompliance with pharmacy certification.

4.4.3 Patients

The Camzyos REMS assessment plan includes metrics on patient enrollment. The Camzyos REMS requirement for patient enrollment supports the objectives *of the need for monitoring for detection of heart failure due to systolic dysfunction with periodic echocardiograms and for screening for drug interactions prior to each dispense*. Enrolled patients confirm being aware of the REMS requirements and the goals of the Mavacamten REMS when they complete the Mavacamten REMS Patient Enrollment Form. The metrics related to patient enrollment provide context for the use of Mavacamten and might allow the review team to assess for evidence of unanticipated burden and problems with access. The collection of gender and age was included to provide additional information on the population since teratogenicity is included in labelling. The team recognizes that this is not an objective of the REMS however it was felt that age and gender might provide important context to understanding the use of the product and support future benefit risk assessments related to the REMS.

4.4.4 Wholesalers-distributors

The Camzyos REMS assessment plan collects metrics on wholesaler-distributors who are authorized to distribute Camzyos. These metrics are collected to provide context for the program including noncompliance and audit information.

4.5 Noncompliance

4.5.1 To support the REMS assessment, the Applicant is required to submit noncompliance and audit plans with each REMS assessment. Noncompliance metrics

The Camzyos REMS assessment plan includes metrics to determine whether dispensing is limited to enrolled patients, based on prescriptions written by certified prescribers, and dispensed by certified

pharmacies. These elements to assure safe use (ETASU), are REMS requirements that the Camzyos REMS team has determined are necessary to ensure the benefit of Camzyos outweighs the risk of heart failure due to systolic dysfunction. Enrolled patients and certified prescribers are informed of the REMS requirements and have attested that they will comply with the requirements to monitor for detection of heart failure due to systolic dysfunction with periodic echocardiograms. Certified prescribers and pharmacy authorized representatives attest that they will screen for drug interactions prior to each dispense. The Camzyos REMS has processes in place to restrict dispensing based on stakeholder certification and/or enrollment. Due to these restrictions, a success rate or threshold of 99.9% for each requirement was agreed to by the Agency and Applicant during the REMS development (see March 9, 2022, comments to the Applicant and Applicant March 21, 2022, REMS submission). This threshold aligns with what is achieved in other stable REMS programs as well as what the Institute for Healthcare Improvement suggests would be achieved for a program that utilizes restrictions and is not dependent on reminders and encouragement to achieve its results when stable.¹ The Applicant's non-compliance plan will be submitted with each REMS assessment.

4.5.2 Audits

The Camzyos REMS document requires the Applicant to: *maintain adequate records to demonstrate that the REMS requirements have been met including... including records of certified pharmacies and wholesaler-distributors*. The Applicant's supporting document identifies that the Applicant "will audit pharmacies no later than 180 calendar days after they become certified and annually thereafter to ensure that all REMS processes and procedures are in place, functioning, and support the Camzyos REMS". The metrics to determine that these requirements are met are collected in the assessment plan. The Applicant's audit plan will be submitted with each REMS assessment.

4.6 Utilization Data

The Camzyos REMS Assessment Plan includes metrics on the number of prescriptions dispensed (authorized) as well as the number of prescriptions denied (not authorized). These metrics provide context for the use of Camzyos and also may allow the review team to assess for evidence of unanticipated burden and problems with access. Prescriptions that are not authorized may act as measures to assess the degree of burden and how the REMS negatively impacts access by causing a delay in obtaining Camzyos that would not occur in the absence of the REMS. Denials associated with missing echocardiogram and incomplete assessment of drug-drug interactions also support that the REMS is ensuring that the objectives of the REMS are being met and may support impact of the REMS on safety.

Safe Use Behavior

4.7 Patient Status Forms

The first objective of the Camzyos REMS is to: *Monitor for detection of heart failure due to systolic dysfunction with periodic echocardiograms*. The Camzyos REMS is designed to accomplish this by restricting dispensing to patients who have had a Camzyos Patient Status Form submitted at the time that echocardiograms are required as described in the Prescribing Information. The metrics collected related to the Camzyos Patient Status Form identify whether the Camzyos Patient Status Forms are complete, the prescriber authorized treatment, as well as other variables that provide context and a

potential measure of burden (patients whose echocardiograms were completed off drug as a result of a pre-dispense authorization denial and potential reasons for this). The Applicant and the Agency have agreed that the *Number of first patient shipments sent prior to receipt of a Patient Enrollment Form (numerator) divided by all patients who were dispensed Camzyos (denominator)* will have a compliance rate of 99.9%.

4.8 Drug Interaction and Counseling Checklist for Pharmacies

The second objective of the Camzyos REMS is to: *Screen for drug interactions prior to each dispense*. The REMS is designed to accomplish this by restricting distribution to patients who have had drug interactions evaluated by the prescriber and documented on the Patient Status Form and by review of drugs and counseling provided by the pharmacy prior to submitting the Drug Interaction and Counseling Checklist (DICC) to the REMS program and receiving authorization to dispense. The metrics collected identify that the DICC is complete, the pharmacy has documented the presence of any medications that are contraindicated or require dose adjustment and that actions based on these results were taken and align with the recommendations in labelling. The Applicant and the Agency have agreed that the *Number of unique patients who had a Drug Interaction and Counseling Checklist completed prior to their initial dispensing of Camzyos (numerator) divided by the number of patients who initiated therapy with Camzyos (denominator)* will have a compliance rate of 99.9%.

4.9 Knowledge Assessment

The Knowledge Assessment for the Camzyos REMS is linked to prescriber certification and pharmacy authorized representative certification. The knowledge assessment consists of ten questions for potential prescribers and ten questions for pharmacy ARs that identify key requirements of the Mavacamten REMS. Both groups of stakeholders are required to successfully complete Knowledge Assessments prior to being certified in the REMS program. The number of completed Knowledge Assessments, method of completion and number of attempts to complete the respective Knowledge Assessments are collected. Additional metrics associated with these requirements are collected to identify any questions in the Knowledge Assessment that require further evaluation related to the adequacy of the knowledge assessment questions and the Camzyos (mavacamten) REMS Education Program for Healthcare Providers and Pharmacies.

4.10 Key Performance Indicator

The Key Performance Indication (KPI) is the measure which is essential in determining the success of the Camzyos REMS program and ensures that the REMS is functioning as designed. Following internal discussion with DMAMES, Division of Risk Management and the Applicant and initially presented to the REMS Oversight Committee on August 21, 2022, as well as communications with the Applicant (March 9, 2022, comments to the Applicant and Applicant March 21, 2022, REMS submission) the following KPI and threshold for success was identified.

The KPI is the number of prescriptions dispensed with an authorization from the REMS program when the prescription:

- i. Will be dispensed from a certified pharmacy
- ii. Is written by a certified prescriber
- iii. Is written for an enrolled patient
- iv. Has a completed Patient Status form that documents an appropriately timed echocardiogram

- v. Has a completed Drug Interaction and Counseling Checklist for Pharmacies that documents appropriate actions were taken prior to authorization

The threshold for the KPI is that 99.9% of dispenses are associated with an approved authorization

5. Conclusion

On April 27, 2022, the Applicant submitted a clean supporting document with an included assessment plan that is acceptable to the Agency and is included in Appendix A: Camzyos (mavacamten) REMS Assessment Plan, and will be included in the approval letter.

6. Appendices

6.1 Appendix A: Camzyos (mavacamten) REMS Assessment Plan

The Camzyos REMS Assessment Plan must include, but is not limited to, the following:

Program Outreach and Communication (provide data at the 1-year assessment only)

1. REMS Program Website
 - a) Date REMS website went live
 - b) Number of total visits and unique visits to the REMS Program Website
 - c) Number and type of Camzyos REMS materials downloaded or accessed

Program Implementation and Operations

2. REMS Call Center Reports (provide data for two previous reporting periods, the current reporting period, and cumulatively)
 - a) Number of calls by stakeholder type (patient, healthcare provider, designee, pharmacy, wholesalers-distributors, other)
 - b) Summary of reasons for calls (e.g., enrollment question) and stakeholder type (patients, healthcare provider, designee, pharmacy, other). Limit the summary to the top five reasons for calls by each stakeholder group.
 - c) If the summary reason for the call(s) indicates a complaint, include details on the nature of the complaint(s) and whether the caller indicated potential REMS burden or patient access issues
 - d) If the summary reason for the call(s) indicates an adverse event related to heart failure or a contraindicated drug or drug interaction, include details and the outcome of the call(s)
 - e) Percentage of calls to the REMS Call Center that were answered within 20 minutes.
 - f) The shortest wait time for a call to be answered, the longest wait time for a call to be answered and the median time for a call to be answered
 - g) Percentage of calls to the REMS Call Center where the caller abandoned the call before the call was answered
 - h) The shortest wait time at which a call was abandoned, the longest wait time before the call was abandoned and the median wait time for a call to be abandoned
3. Program Implementation (provide data at the 1-year assessment only)

- a) Date of first commercial availability of Camzyos
 - b) For each stakeholder (healthcare providers, designees, pharmacies, patients), the date when they could become certified
 - c) Date when the Camzyos REMS Call Center was established and fully operational
- 4. REMS Certification and Enrollment (provide data for two previous reporting periods, the current reporting period and cumulatively)
 - a) Healthcare Providers
 - i. Number of newly certified healthcare providers and number of active (i.e., who have prescribed at least once during the reporting period) healthcare providers stratified by credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other), specialty (e.g., Cardiology, Electrophysiology, Geneticist, Other), and geographic region (defined by US Census). If “Other” accounts for >10% of respondents, provide the most common specialties identified. Specifically identify and categorize if a specialty is within cardiology or non-cardiology.
 - b) Number of Designees stratified by role (e.g., RPh/PharmD, RN, NP, or PA).
 - i. Method of healthcare provider and designee certification (online or fax).
 - c) Pharmacies
 - i. Number of newly certified pharmacies
 - ii. Number of active pharmacies (i.e., have dispensed Camzyos)
 - d) Patients
 - i. Number of newly enrolled patients and number of active (i.e., received at least one dispense of Camzyos) patients stratified by a combined variable of age and gender and geographic region. Provide the minimum and maximum age of enrolled patients. For gender/age variable use age ranges of less than 18, 18-40, 41-60, 61 and older
 - e) Wholesalers-distributors
 - i. Number of newly contracted wholesalers-distributors and number of active (i.e., have shipped Camzyos) wholesalers-distributors.
- 5. REMS Compliance (provide data for two previous reporting periods, the current reporting period, and cumulatively)
 - a) A copy of the non-compliance plan, including the criteria for non-compliance for healthcare providers, pharmacies, and wholesalers-distributors, actions taken to address noncompliance for each case, and which event lead to decertification from the Camzyos REMS (Beginning with the 1-year assessment and annually thereafter)
 - b) Audits
 - i. A copy of the audit plan for pharmacies and wholesalers/distributors
 - ii. Report of audit findings for each stakeholder (pharmacies and wholesalers-distributors)
 - iii. Number of audits expected, and the number of audits performed.
 - iv. Documentation of completion of training for relevant staff.
 - v. Documentation of processes and procedures in place for complying with the Camzyos REMS.
 - vi. Verification for each audited stakeholder’s site that the designated Authorized Representative remains the same. If different, document that the pharmacy has re-certified with the name and contact information for the new Authorized Representative.

- vii. Number and types of deficiencies noted for each group of audited stakeholders as a percentage of audited stakeholders.
 - viii. For each Audited Pharmacy, number of the following deficiencies (numerator) divided by the number of dispenses audited at that pharmacy (denominator):
 - 1. Healthcare provider not certified, and prescription dispensed
 - 2. Patient not enrolled and prescription dispensed
 - 3. Drug Interaction and Counseling Checklist not completed, and prescription dispensed
 - 4. Audit of Drug Interaction and Counseling Checklist forms that identified a drug was dispensed but a required action not taken
 - 5. Authorization denied and prescription dispensed
 - ix. For stakeholders with deficiencies noted, the number that successfully completed a Corrective and Preventative Action (CAPA) plan and as a percentage of those for which a CAPA plan was requested.
 - x. For any stakeholders who did not complete the CAPA Plan, a description of actions taken.
- c) Healthcare provider noncompliance (For each non-compliance event, the source of the report, a description of the event, the root cause analysis of the event, and corrective actions taken)
- i. Number of healthcare providers who were non-compliant with the Camzyos REMS program requirements. Provide as a percentage of active healthcare providers.
 - ii. Number of healthcare providers who were de-certified and reasons for de-certification also provide as a percentage of active healthcare providers. Include if any healthcare providers were re certified.
- d) Pharmacies (For each non-compliance event, the source of the report, a description of the event, the root cause analysis, and corrective actions taken)
- i. Number of pharmacies for which non-compliance with the Camzyos REMS is detected (numerator) divided by all pharmacies dispensing Camzyos (denominator)
 - ii. The number of non-certified pharmacies that dispensed Camzyos (numerator) divided by all pharmacies that dispensed Camzyos (denominator). A compliance rate of 99.9% is expected.
 - iii. Number of Camzyos prescriptions dispensed by non-certified pharmacies (numerator) divided by all prescriptions Camzyos dispensed (denominator) and the actions taken to prevent future occurrences. A compliance rate of 99.9% is expected.
 - iv. Number of Camzyos prescriptions dispensed that were written by non-certified healthcare providers (numerator) divided by all dispensed prescriptions (denominator). For prescriptions dispensed that were written by non-certified healthcare providers, provide the root cause analysis and the actions taken to prevent future occurrences. A compliance rate of 99.9% is expected.
 - v. Number of Camzyos prescriptions dispensed to non-enrolled patients (numerator) divided by all dispensed prescriptions (denominator). For prescriptions dispense to non-enrolled patients provide a root cause analysis and the actions taken to prevent future occurrences. A compliance rate of 99.9% is expected.
 - vi. Number of Camzyos prescriptions dispensed to non-enrolled patients based on a prescription from a non-certified healthcare provider (numerator) divided by all

- dispensed prescriptions (denominator). For prescriptions dispensed to non-enrolled patients based on a prescription from a non-certified healthcare provider provide a root cause analysis and the actions taken to prevent future occurrences. A compliance rate of 99.9% is expected.
- vii. Number of times a Camzyos prescription was dispensed because a certified pharmacy bypassed the Camzyos REMS authorization processes (numerator) divided by all certified pharmacies (denominator). Provide a root cause analysis and including a description of how the events were identified and any corrective actions taken. A compliance rate of 99.9% is expected.
 - viii. Number of pharmacies decertified, reasons for decertification, and actions to address non-compliance. Provide as a ratio the number of pharmacies decertified (numerator) divided by all certified pharmacies (denominator)
- e) Wholesalers-distributors (For each non-compliance event, the source of the report, a description of the event, the root cause analysis, and corrective actions taken)
- i. Number of contracted wholesalers-distributors for which non-compliance with the Camzyos REMS is detected (numerator) divided by the number of contracted wholesalers-distributors (denominator)
 - ii. Number of wholesalers-distributors suspended from distributing, reasons for the suspension, and actions to address non-compliance
 - iii. Number of times Camzyos was distributed to a non-certified pharmacy (numerator) divided by the number of distributions of Camzyos (denominator)
6. Utilization Data (provide data for two previous reporting periods, the current reporting period, and cumulatively)
- a) Number of prescriptions (new and refills) dispensed, stratified by:
 - i. Healthcare provider degree/credentials and geographic region
 - ii. Patient demographics (age and gender, and geographic region)
 - b) The number of prescriptions received and denied (not authorized), stratified by:
 - i. Reasons and number of denials (numerator) divided by all denials (denominator)
 - 1. Healthcare provider not certified
 - 2. Prescription written by designee.
 - 3. Patient not enrolled
 - 4. Patient status form documenting echocardiogram not submitted on appropriate schedule
 - 5. Drug Interaction and Counseling Checklist-not completed
 - 6. Drug interaction or contraindicated drug identified, and appropriate actions not taken
 - 7. Other reasons for denial not categorized above
 - ii. Healthcare provider degree/credentials and geographic region
 - c) Number of unique healthcare providers who wrote prescriptions dispensed in the reporting period (active healthcare providers)
 - d) Number of unique patients receiving Camzyos, stratified by age, gender, and geographic region
7. Burden to the Healthcare System and/or Barriers to Patient Access
- a) Reports to the Camzyos REMS Call Center indicating a burden to the healthcare system or barriers to patient access. Assessment of whether burden is attributable to the REMS,

insurance, health care availability, other

Safe Use Behavior

8. Patient Status Forms (provide data for two previous reporting periods, current reporting period and cumulatively)
 - a) Number of Patient Status Forms expected, received, and outstanding as of the REMS assessment cut-off date
 - b) Number of first patient shipments sent prior to receipt of a Patient Enrollment Form (numerator) divided by all patients who were dispensed Camzyos (denominator). A compliance rate of 99.9% is expected.
 - c) Number of unique patients who had a Patient Status Form submitted who the healthcare provider confirmed reviewing the echocardiogram for (numerator) divided by number of unique patients who had a Patient Status Form submitted (denominator)
 - d) Number of unique patients who had a Patient Status Form submitted who the healthcare provider authorized treatment for (numerator) divided by number of unique patients who had a patient status form submitted (denominator)
 - e) Number of Patient Status Forms outstanding from previous reporting periods that were completed in the current reporting period (numerator) divided by the number of outstanding Patients Status Forms from the previous reporting period (if applicable)
 - f) Number of patients whose echocardiogram was completed off drug as a result of an authorization denial and reason (e.g., drug not dispensed due to missing Patient Status Form, insurance issues prevented drug dispensing, transportation issues prevented patient from obtaining echocardiograms)
 - g) Number of Patient Status Forms on which the healthcare provider indicated that the patient experienced a clinical heart failure event requiring hospitalization
 - i. Number of Patient Status Forms-on which the healthcare provider indicated the patient experienced a decrease in LVEF to <50%
 - h) Number of patients who were not authorized to receive Camzyos as indicated on the Patient Status Form
9. Drug Interaction and Counseling Checklist for Pharmacies (provide data for two previous reporting periods, current reporting period and cumulatively)
 - a) Number of unique patients who had a Drug Interaction and Counseling Checklist completed prior to their initial dispensing of Camzyos (numerator) divided by the number of patients who initiated therapy with Camzyos (denominator). Compliance rate of 99.9%.
 - b) Number of prescriptions dispensed that had a Drug Interaction and Counseling Checklist completed prior to dispensing (numerator) divided by the number of prescriptions dispensed for Camzyos (denominator). A compliance rate of 99.9% is expected.
 - c) Number of Drug Interaction and Counseling Checklist that identified a concurrent contraindicated medicines (numerator) divided by the total number of Drug Interaction and Counseling Checklists completed (denominator)
 - d) For those Drug Interaction and Counseling Checklists that identified a concurrent contraindicated medicines indicate the source of the drug interaction and action taken after healthcare provider was contacted including:
 - i. Source
 1. Interacting drug prescribed by Camzyos certified healthcare

- provider/designee
 - 2. Interacting drug prescribed by other healthcare provider
 - 3. Interacting drug purchased over the counter by patient
 - ii. Action taken
 - 1. Camzyos discontinued
 - 2. Contraindicated drug discontinued
 - e) Number of Drug Interaction and Counseling Checklist that identified a concurrent medicine that required a dosage reduction (numerator) divided by the total number of Drug Interaction and Counseling Checklists completed (denominator).
 - f) For those Drug Interaction and Counseling Checklist that identified a concurrent medicine that required a dosage reduction indicate source of drug interaction and action taken after healthcare provider was contacted including:
 - i. Source
 - 1. Interacting drug prescribed by Camzyos certified healthcare provider/designee
 - 2. Interacting drug prescribed by other healthcare provider
 - 3. Interacting drug purchased over the counter by patient
 - ii. Action taken
 - 1. Camzyos discontinued
 - 2. Camzyos dose decreased
 - 3. Other medicine(s) discontinued
 - g) Any information obtained from audits, or self-reported by pharmacies that indicated that a patient did receive a contraindicated medicine, while taking Camzyos expressed by the number of patients who received at least one shipment (dispensing) of Camzyos who were also taking a concurrent contraindicated medicine (numerator) divided by the total number of patients with at least one shipment (dispensing) of Camzyos (denominator)
 - i. For all occurrences, include the contraindicated drug name, dose, and duration of therapy
10. Knowledge Assessments (provide data at the 1-year and 2-year assessment reports only)
- a) Number of completed Healthcare Provider Knowledge Assessments, including the method of completion and number of attempts to complete
 - b) A summary of the most frequently missed Healthcare Provider Knowledge Assessment questions
 - c) A summary of potential comprehension or perception issues identified with the Healthcare Provider Knowledge Assessment
 - d) Number of completed Pharmacy Authorized Representative Knowledge Assessments, including the method of completion and number of attempts to complete
 - e) A summary of the most frequently missed Pharmacy Authorized Representative Knowledge Assessment questions
 - f) A summary of potential comprehension or perception issues identified with the Pharmacy Authorized Representative Knowledge Assessment
11. Report on Key Performance Indicator (KPI)
- a) The KPI is the number of prescriptions dispensed with an authorization from the REMS program when the prescription:
 - i. Will be dispensed from a Certified pharmacy
 - ii. Written by a Certified prescriber

- iii. Written for an Enrolled patient
- iv. Has a completed Patient Status form that documents an appropriately timed echocardiogram
- v. Has a completed Drug Interaction and Counseling Checklist that documents appropriate actions were taken prior to authorization.

The threshold for the KPI is that 99.9% of dispenses are associated with an approved authorization

Overall Assessment of REMS (b) (4)

- 12. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

7. References

- 1. T. Nolan, R. Resar, C. Harden. Improving the Reliability of Health Care. In: *IHI Innovation Series White Paper*. Boston: Institute for Healthcare Improvement; 2004.

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/s/

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Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Division of Cardiology and Nephrology**

NDA/BLA #s: 214998
Products: Camzyos (mavacamten)
APPLICANT: Myocardia
FROM: Hylton V. Joffe, MD, MMSc, OCHEN Director
DATE: 4/28/2022

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Camzyos (mavacamten) to ensure that the benefits of the drug outweigh the risks of heart failure due to systolic dysfunction. In reaching this determination, we considered the following:

- A. The prevalence of asymptomatic HCM among young adults in the United States has been estimated at 1/200 to 1/500, with symptomatic HCM being less common based on medical claims data (estimated at < 1:3000).
- B. Hypertrophic cardiomyopathy (HCM) is a genetic myocardial disorder characterized by left ventricular (LV) hypertrophy, hyperdynamic contraction and impaired relaxation. Patients with oHCM have diverse clinical symptomatology (chest pain, syncope, fatigue) and disease courses and are at increased risk of developing other cardiac comorbidities and sudden cardiac death. Most hypertrophic cardiomyopathy patients can expect a normal lifespan; however, the presence of symptoms is associated with worse outcomes.
- C. Camzyos (mavacamten) has demonstrated an improvement in functional capacity and symptoms.
- D. The drug would be expected to be used chronically.
- E. Camzyos (mavacamten) produces a reduction in myocardial contractility and can cause heart failure.
- F. Camzyos (mavacamten) is a new molecular entity (NME).

The elements of the REMS will include elements to assure safe use. The elements to assure safe use include:

- Healthcare providers must undergo training and be certified in order to prescribe this drug.
- Pharmacies and other facilities that dispense Camzyos (mavacamten) must be certified.
- Camzyos (mavacamten) will be dispensed only with documentation of safe use conditions.
- Patients will have echocardiograms performed at scheduled intervals.

The elements of the REMS will also include an implementation system and a timetable for submission of assessments of the REMS.

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214998
PDUFA Goal Date	April 28, 2022
OSE RCM #	2021-191
Reviewer Name(s)	Courtney Cunningham, PharmD Kate Heinrich Oswell, M.A.
Associate Director for REMS	Laura Zendel, PharmD
Design and Evaluation	
Review Completion Date	April 21, 2022
Subject	Evaluation of the Proposed REMS
Established Name	Mavacamten
Trade Name	Camzyos
Name of Applicant	Bristol Myers Squibb
Therapeutic Class	Cardiac Myosin Inhibitor
Formulation(s)	2.5, 5, 10, and 15 mg oral capsules
Dosing Regimen	Starting dose 5 mg daily: may increase 12 weeks after initiation based on PD markers

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4	Appendices	6
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1. Introduction

This review evaluates the risk evaluation and mitigation strategy (REMS) amendment submitted on April 18, 2022, for the new molecular entity (NME)^a Camzyos (mavacamten). Myokardia, a wholly-owned subsidiary of Bristol Myers Squibb submitted a New Drug Application (NDA 214998) for mavacamten with the proposed indication for the treatment of symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) in adults to improve functional capacity, (b) (4) and symptoms. This application is under review in the Division of Cardiology and Nephrology (DCN). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of mavacamten outweigh the risk of heart failure due to systolic dysfunction.

2. Background

2.1 REGULATORY HISTORY

The following is a summary of the regulatory history for mavacamten NDA 214998 relevant to this review:

- 04/08/2022: DRM sent Interim Comments and redlined REMS materials to the Applicant with an acknowledgement that edits to the REMS Document and stakeholder attestations would be forthcoming.¹
- 04/11/2022, 04/13/2022: DRM sent updated REMS Documents and attestations including using Myokardia, Inc. as the application holder and Bristol Myers Squibb as the parent company to which adverse events should be reported, as well as global updates to the REMS Document and attestations from the Agency.^{2,3}
- 4/18/2022: Applicant submitted a REMS Amendment in response to DRM's comments

3. Comments for the Applicant

The following comments and attached redlined Camzyos Risk Evaluation and Mitigation Strategy (REMS) materials are based on our review of the proposed REMS submitted by Bristol Myers Squibb on April 18, 2022. To facilitate further review, please address the following comments and resubmit your complete REMS (clean and redlined Word versions and clean pdf versions of the REMS Document and all materials) as an amendment by April 25, 2022. These comments should not be considered as final edits to the REMS.

^a Section 505-1(a) of the FD&C Act: *FDAAA factor (F)*: Whether the drug is a new molecular entity

General Comments and Information Requests:

- The REMS document and attestations have been cleared by the Agency. Additional proposed changes may result in delay of approval of your proposed REMS. Redlined versions of the REMS Document and materials are attached. We have made multiple edits for content and clarity. Please address all edits and comments from the Agency in your redlined materials and cover letter if necessary.
- All REMS materials, including text and graphics, must be revised to be consistent with the final approved labeling and resubmitted for review.
- Align print and electronic versions of enrollment forms and educational materials.
- The next submission should include all changes and edits noted on the redlined materials and in the comments. The complete submission, including redlined and clean Word documents and clean pdf versions must be formally submitted to the Agency by 1 pm EST Monday, April 25, 2022.
- Include “rapid weight gain” in all materials that list heart failure symptoms for patients. This is to align with the symptom list in the current Medication Guide.

REMS Document

- Incorporate the full name “Myokardia, Inc.” throughout the document.
- The timeline for REMS requirements for stakeholders is edited from (b) (4) to “dose change” to align with requirements in labeling.
- “Supplements” have been added to the healthcare provider requirements to align with the patient requirements.
- Incorporate these changes through all REMS materials.

Healthcare Provider, Pharmacy Authorized Representative, and Patient Attestations

- We have provided updated stakeholder attestations. Please incorporate these into all appropriate REMS materials, including the Supporting Document.
- See redlined attestations for necessary inclusion of “Camzyos REMS” to replace (b) (4) the inclusion of “rapid weight gain” into list of heart failure symptoms to align with the Medication Guide, and to align with the REMS Document.

REMS Supporting Document

- Align the Supporting Document with edits made to the REMS Document and include the most recent Assessment Plan.

- Both the *HCP and Pharmacy Portal* and *Designee Enrollment Form* should be appended to the Supporting Document in the next submission.

Healthcare Provider, Patient, and Pharmacy Enrollment Forms

- Add attestations for each stakeholder that are provided with these comments.
- In the Patient Enrollment Form, add “alternate” to the optional phone number to provide more context for requesting a second phone number from patients.

Healthcare Provider Designee Enrollment Form

- In the upcoming submission, append this material to the Supporting Document.
- Update the attestations per the Agency edits to reflect the designee’s responsibilities, including cardiovascular assessment.

Program Overview

- Edit to align with the updated REMS Document (i.e., the use of “dose changes” instead of (b) (4)) and attestations.

Education Program for Healthcare Providers and Pharmacies

- Continue to align the content of the *Education Program* with the current label and REMS Document.
- The current Slide 18 should be moved back before the current Slide 17 outlining counseling, as designees may counsel and should review that information.
- In the ECHO assessment timelines, 12 week monitoring is often denoted as (b) (4) As “12 weeks” is used in labeling and REMS Document, replace all instances of (b) (4) with “12 weeks.”

Healthcare Provider Knowledge Assessment

- Align all language with current labeling.

Pharmacy Authorized Representative Knowledge Assessment

- See the redlined document for edits to align Question 7 with directions on the *Drug Interaction and (b) (4) Counseling Checklist* and incorporate current labeling as updates.

Patient Brochure

- Reformat the PDF so that pages 2 and 3 print out as separate pages and the complete file prints as 4 separate pages, as in the previous submission. Current formatting does not allow a pharmacist or healthcare provider to print out the brochure on standard letter sized paper without cutting off pages 2 and 3.

- Include “rapid weight gain” in the list of heart failure symptoms for patients to be aware of. This is to align with the Medication Guide.

Drug Interaction and Counseling Checklist for Pharmacies

- As the pharmacist will not have access to the “other” reason the dose of Camzyos was decreased, we have added the clarifier “not listed on the *Patient Status Form* for clarity and to avoid multiple calls to the healthcare provider/designee.
- We have revised the statement regarding initiation of Camzyos in the presence of moderate CYP3A4 inhibitors or weak CYP2C19 inhibitors for clarity and to align with labeling.
- Include “rapid weight gain” in the list of example symptoms of heart failure.

REMS Program Website

- Apply all edits and align all REMS materials on the website with the print versions.

Website Stakeholder Portals

- The next submission of screenshots should show portal capabilities in complete pages and content as screenshots in PDF files. We do not need to see tracked changes in a Word document.
- Remove [REDACTED] (b) (4) [REDACTED]. This information is to be included in the Camzyos REMS Supporting Document.
- Apply changes from print materials to the REMS website and portal.

4. Appendices

4.1 REFERENCES

1. Cunningham, C. Division of Risk Management Interim Comments on the Proposed Mavacamten (NDA 214998) REMS, April 8, 2022, DARRTS ID# 4966211
2. Cunningham, C. updated Camzyos REMS Document and attestations sent to Bristol Myers Squibb in email correspondence, April 11, 2022.
3. Cunningham, C., updated Camzyos REMS Document and attestations sent to Bristol Myers Squibb via email correspondence, April 13, 2022.

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/s/

COURTNEY A CUNNINGHAM
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KATE H OSWELL
04/21/2022 11:44:54 AM

LAURA A ZENDEL
04/21/2022 12:24:36 PM

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214998
PDUFA Goal Date	April 28, 2022
OSE RCM #	2021-191
Reviewer Name(s)	Courtney Cunningham, PharmD Katherine Hyatt Hawkins Shaw, PhD Kate Heinrich Oswell, M.A.
Associate Director for REMS	Laura Zendel, PharmD
Design and Evaluation	
Review Completion Date	April 08, 2022
Subject	Evaluation of the Proposed REMS
Established Name	Mavacamten
Trade Name	Camzyos
Name of Applicant	Bristol Myers Squibb
Therapeutic Class	Cardiac Myosin Inhibitor
Formulation(s)	2.5, 5, 10, and 15 mg oral capsules
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1. Introduction

This review evaluates the risk evaluation and mitigation strategy (REMS) amendment on March 21, 2022, for the new molecular entity (NME)^a Camzyos (mavacamten). Bristol Myers Squibb submitted a New Drug Application (NDA 214998) for mavacamten with the proposed indication for the treatment of symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) in adults to improve functional capacity, (b) (4) and symptoms. This application is under review in the Division of Cardiology and Nephrology (DCN). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of mavacamten outweigh the risk of heart failure due to systolic dysfunction.

2. Background

2.1 REGULATORY HISTORY

The following is a summary of the regulatory history for mavacamten NDA 214998 relevant to this review:

- 03/02/2022: The Division of Risk Management (DRM) sent Interim Comments and redlined Camzyos REMS materials to Bristol Myers Squibb, with a notification that edits to the Camzyos REMS Assessment Plan would be forthcoming.¹
- 03/09/2022: DRM sent an addendum to the March 2, 2022, Interim Comments that included additional Interim Comments and a redlined Camzyos REMS *Drug Interaction and Counseling Checklist for Pharmacies* to align with the Division of Mitigation and Medication Error Surveillance (DMAMES) comments and redlined Camzyos Assessment Plan sent with the DRM amendment.^{2,3}
- 03/14/2022: DRM, DMAMES, DCN, and Bristol Myers Squibb participated in a teleconference to discuss the Interim Comments sent by the Agency on March 2 and 9, 2022

3. Discussion

On March 14, 2022, DRM, DMAMES, DCN, and Bristol Myers Squibb participated in a teleconference to discuss the interim comments sent by the Agency on March 2 and 9, 2022. Topics discussed included (b) (4), including baseline echocardiogram information on the *Patient Enrollment Form* for the first dispense of mavacamten, Bristol Myers Squibb's proposal that physicians should be able to override the 'hard stop' to dispensing mavacamten in the case of drug-drug interactions or contraindicated medications and how much data was appropriate and necessary to collect on the *Drug Interaction and Counseling Checklist for Pharmacies* to assist pharmacists in decision-making.

^a Section 505-1(a) of the FD&C Act: *FDAAA factor (F)*: Whether the drug is a new molecular entity

The Agency and Bristol Myers Squibb (BMS) concurred (b) (4), while beneficial, was not a necessity at this time. (b) (4) BMS incorporated a calendar with reminders when *Patient Status Forms* are upcoming, eligible for submission, and overdue. This can be accessed by both healthcare providers and their designees. The Agency and BMS also agreed that questions related to a patient's baseline echocardiogram and drug interaction screenings could be incorporated into the *Patient Enrollment Form* (b) (4) so healthcare providers will submit a single form for enrollment and confirmation of baseline echocardiogram review. After discussion regarding the implementation of 'hard stops' due to contraindicated or require dose adjustments, the Agency's position remains that dosing with mavacamten must be lowered appropriately, or the contraindicated/interacting drug stopped prior to continuing mavacamten treatment and these 'hard stops' are necessary to ensure the benefits of Camzyos outweigh the risk. BMS agreed and proposed incorporating this into the pharmacy portal by requiring pharmacists to attest they have submitted the *Drug Interaction and Counseling Checklist for Pharmacies*. During our review, we determined that the *Checklist* should be incorporated into the pharmacy workflow in the portal and submitted before an authorization to dispense is provided to the pharmacist. The Agency's position is that giving pharmacists full access to information on the *Patient Status Form* that explains why a dose has changed will assist them in the decision-making process, in line with pharmacy workflow. Without including this information on the form, it may create an extra step for the pharmacists to contact the healthcare provider to obtain information to ensure the safe use conditions of dispensing of mavacamten are met. BMS included the pertinent information in the pharmacy portal. ⁴

4. Comments for the Applicant

The following comments and attached redlined Camzyos Risk Evaluation and Mitigation Strategy (REMS) materials are based on our review of the proposed REMS submitted by Bristol Myers Squibb on March 21, 2022. To facilitate further review, please address the following comments and resubmit your complete REMS (clean and redlined Word versions and clean pdf versions of the REMS Document and all materials) as an amendment by April 15, 2022. These comments should not be considered as final edits to the REMS.

General Comments and Information Requests:

- Redlined versions of the REMS materials are attached. We have made numerous edits for content and clarity. Please address all edits and comments from the Agency in your redlined materials and cover letter if necessary.
- All REMS materials, including text and graphics, must be revised to be consistent with the final approved labeling and resubmitted for review.
- Align print and electronic versions of enrollment forms and educational materials.
- Align the Assessment Plan that is included in these redlined materials with any changes in the current REMS materials; in the upcoming submission, incorporate the Assessment Plan into the appropriate section of the Supporting Document.

REMS Document

- We will be sending a REMS Document that is based on the Agency’s ongoing review of the proposed Camzyos REMS.
- Currently, it is stated that training for healthcare providers and pharmacies will be available via email, online, and in hard copy via mail. Please edit if that method is not correct.

Healthcare Provider, Pharmacy Authorized Representative, and Patient Attestations

- We will be sending attestations for stakeholders. Please incorporate these attestations into all appropriate REMS materials, including the Supporting Document.

REMS Supporting Document

- Align the Supporting Document with edits made to the REMS Document and all REMS materials, including the most recent Assessment Plan.
- On Page 13, provide a timetable as to when healthcare providers will be reminded prior to and after the due date of the Patient Status Form.

Healthcare Provider Enrollment Form

- Incorporate attestations for healthcare providers.
- Include form title on all pages to avoid confusion if form is faxed in.
- “Signature” and “Date” should be bolded to avoid being overlooked.

Healthcare Provider Designee Enrollment Form

- In the final submission, this material should be appended to the Supporting Document.
- We added a line to remind both the certified healthcare provider signing the form and the certified healthcare provider’s designee that all prescriptions for Camzyos must be written by a certified healthcare provider, even though the designee may have prescribing privileges.
- Bold “Designee” in the “Designee Signature” field on the pdf version.

Patient Enrollment Form

- Replace (b) (4) in the Patient Information boxes with “Gender.”
- Incorporate attestations for patients.
- We’ve added a clarifying LVEF value to the Healthcare Provider Acknowledgement section to align with labeling and remind healthcare providers of recommended starting LVEF.
- Include form title on all pages to avoid confusion if form is faxed in.
- “Signature” and “Date” should be bolded to avoid being overlooked.

Pharmacy Enrollment Form

- Incorporate attestations for Pharmacy Authorized Representative.
- Include form title on all pages to avoid confusion if form is faxed in.
- “Signature” and “Date” should be bolded to avoid being overlooked.

Program Overview

- Edit to align with the updated REMS Document and attestations.
- As MyoKardia is a subsidiary of Bristol Myers Squibb, reporting of adverse events, etc., will be to Bristol Myers Squibb as per the label. Update the *Program Overview* to reflect this throughout.

Education Program for Healthcare Providers and Pharmacies

- Align the content of the *Education Program* with the current draft label and draft REMS Document. The risk information section should focus more on the risk. Content in slide 5 has been replaced with information in the Boxed Warning.
- See redlines for updated formatting of the slides to provide visual breaks in content, call out significant text, and align type. The slides for Healthcare Providers and their Designees have also been split to call out designees and their roles in the REMS.
- See redlines for example to emphasize that all prescriptions need to be written by a certified healthcare provider
- See redlined case scenario slides to better show the timing of activities related to dosing and monitoring.
- Pharmacy certification and dispensing requirements have been split into multiple slides for readability and Camzyos shipping information has been included.

Healthcare Provider Knowledge Assessment

- Align all language with current draft labeling.

Pharmacy Authorized Representative Knowledge Assessment

- See the redlined document for minor edits and continue to align the questions with current draft labeling as updates occur.

Patient Brochure

- “Medicines” should replace (b) (4) throughout the material as it is the most current patient friendly term.
- The order of headings on the Word version of the Patient Brochure varies from that on the pdf version. Please Agency’s redlined edits into the pdf version.

Patient Status Form

- Add the heading “CAMZYOS REMS Patient Status Form” with blue background to pages 2 and 3 of the pdf version to avoid confusion if faxed to the REMS program.
- Bold the signature and date lines under the questions on the *Patient Status Form* to ensure healthcare providers/designees do not skip over the signature line. Consider a “signature required” headline.

Drug Interaction and Counseling Checklist for Pharmacies

- In the text following the second checkbox under Step 3, add “or prior to stopping any medication” to ensure pharmacists counsel patients of this necessity due to drug interactions with CYP2C19 or CYP3A4 inducers.
- Incorporate the examples of contraindicated/interacting medications into the appropriate inducer/inhibitor category in the bulleted list. Example: “Moderate CYP2C19 Inhibitors: *DRUG X*, *DRUG Y*, *DRUG Z*.”

REMS Program Website

- Align all REMS materials on the website with the print versions.
- On the patient landing page, bold the following language in the 4th paragraph: “Tell your healthcare provider about all the medicines you take.”
- Change the language (b) (4) to “medicines.”

Website Stakeholder Portals

- The portal should incorporate the safe use conditions including the *Patient Status Form* and *Drug Interaction and Counseling Checklist* as part of the steps within the portal, instead of separate actions one can take on the portal. In addition, the *Drug Interaction and Counseling Checklist* should be incorporated into workflow prior to “Log Dispense,” as that must be completed and submitted to receive a dispense authorization.
- Include screenshot of home screens including drop down menu options for healthcare providers, designees, authorized representatives and pharmacists. For example: show the drop-down options such as “complete a *Patient Status Form*” for designees as other screen shots note it may be completed on the home screen. Add screenshots of how pharmacy staff create and use an account; include dashboard screenshots and step by step instructions as done with healthcare providers and delegates.
- If a healthcare provider, designee, or pharmacist logs on to the portal, does their information prepopulate on materials and enrollment forms?

- If Camzyos is to be dispensed from specialty pharmacies, why are the options “dispense” and “ship” included in the pharmacy portal?
- The next submission of screenshots should also show portal capabilities for each audience (healthcare providers, designees, authorized representatives and pharmacists) in complete pages and content with step-by-step screenshots in PDF files. We do not need to see tracked changes in a Word document.

5. Appendices

4.1 REFERENCES

1. Cunningham, C., Division of Risk Management Interim Comments on the Proposed Camzyos (mavacamten, NDA 214998) REMS, March 2, 2022, DARRTS ID# 4945947.
2. Jones, Charlotte T., Division of Medication Error Prevention and Analysis Comments on the Proposed Camzyos (mavacamten, NDA 214998) REMS Assessment Plan, March 9, 2022, DARRTS ID# 4949989.
3. Cunningham, C., Division of Risk Management Interim Comments on the Proposed Camzyos (mavacamten NDA 214998) REMS, March 9, 2022, DARRTS ID# 4949882.

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/s/

COURTNEY A CUNNINGHAM
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KATE H OSWELL
04/08/2022 01:38:23 PM

KATHERINE E HYATT HAWKINS SHAW
04/08/2022 01:46:30 PM

LAURA A ZENDEL
04/08/2022 02:24:20 PM

Internal Consult

Pre-decisional Agency Information

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Kate Heinrich Oswell, Health Communications Analyst, DRM
Division of Risk Management (DRM)
Office of Surveillance and Epidemiology (OSE)

From: Charuni Shah, Regulatory Review Officer

CC: Melinda Wilson, Team Leader
Deveonne Hamilton-Stokes, Safety Regulatory Project Manager, OSE
Cynthia LaCavita, Team Leader, DRM
Till Olickal, Risk Management Analyst, DRM
Kate Heinrich Oswell, Health Communications Analyst, DRM
Doris Auth, Associate Director, DRM
Jina Kwak, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: April 07, 2022

Re: NDA 214998
CAMZYOS (mavacamten) capsules for oral use (Camzyos)
Comments on draft Risk Evaluation and Mitigation Strategies (REMS)
Materials

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for Camzyos:

- Healthcare Provider (HCP) REMS Materials:

- [REDACTED] (b) (4)

- Healthcare Provider Knowledge Assessment
 - Healthcare Provider Enrollment Form
 - Education Program for Healthcare Providers and Pharmacies
 - REMS Program Overview
 - Pharmacy Authorized Representative Knowledge Assessment
 - (b) (4)
 - Pharmacy Enrollment Form
 - Patient Status Form
- Direct-to-Consumer (DTC)(Patient) REMS Materials:
 - Patient Enrollment Form
 - Patient Brochure
 - HCP and DTC (Patient) REMS Materials:
 - Camzyos REMS Website

The version of the draft REMS materials used in this review were sent from Kate Oswell, via email, on February 23, 2022. An update to the Education Program for Healthcare Providers and Pharmacies was submitted on March 31, 2022. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Camzyos.

General Comments

Please remind the sponsor that REMS materials are not appropriate for use in a promotional manner.

OPDP notes links such as www.CAMZYOSREMS.com and toll-free numbers such as 1-833-628-7367. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind Bristol Myers Squibb that the REMS specific website should not be the sole source of approved REMS materials.

Comments are provided using the draft product labeling (PI) and Medication Guide (MG) for Camzyos dated March 29, 2022.

OPDP notes that the current Camzyos PI and MG are still being reviewed by DCN. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved label for Camzyos.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see "Specific Comments" below):

- (b) (4)
- Healthcare Provider Knowledge Assessment
- Healthcare Provider Enrollment Form
- Education Program for Healthcare Providers and Pharmacies
- REMS Program Overview
- Pharmacy Authorized Representative Knowledge Assessment
- (b) (4)
- Pharmacy Enrollment Form
- Patient Status Form
- Patient Enrollment Form
- Patient Brochure
- Camzyos REMS Website

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising them in the REMS pieces:



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CHARUNI P SHAH
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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214998
PDUFA Goal Date	April 28, 2022
OSE RCM #	2021-191
Reviewer Name(s)	Courtney Cunningham, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Division Director	Laura Zendel, PharmD
Review Completion Date	March 09, 2022
Subject	Evaluation of the Proposed REMS
Established Name	Mavacamten
Trade Name	Camzyos
Name of Applicant	Bristol Myers Squibb
Therapeutic Class	Cardiac Myosin Inhibitor
Formulation(s)	2.5, 5, 10, and 15 mg oral capsules
Dosing Regimen	Starting dose 5 mg daily: may increase 12 weeks after initiation based on PD markers

1. Introduction

This serves as an addendum to the March 2, 2022, Division of Risk Management (DRM) review¹ that evaluated the risk evaluation and mitigation strategy (REMS) amendment submitted by Bristol Myers Squibb on January 25, 2022, for the new molecular entity (NME)^a Camzyos (mavacamten). DRM and the Division of Mitigation Assessments and Medication Error Surveillance (DMAMES) met on February 24, March 1, and March 3, 2022, to discuss the Assessment Plan for the Camzyos REMS. Following the discussions, DRM and DMAMES agreed that the following metrics would be necessary to successfully assess this REMS program and need to be collected on the *Drug Interaction and* (b) (4) *Checklist*: the number of *Drug Interaction and* (b) (4) *Counseling Checklists* that identified a concurrent contraindicated medication or medication that required a dose adjustment, the source of the medication or supplement, and the action taken after identification. DRM recommends the comments in section 2 be sent to the Applicant concurrently with the DMAMES Camzyos REMS Assessment Plan edits to align the *Drug Interaction and* (b) (4) *Counseling Checklist* with DMAMES' edits to the Camzyos REMS Assessment Plan.

2. Comments for the Applicant

The following comments and attached redlined *Drug Interaction and* (b) (4) *Counseling Checklist* is based on the Division of Risk Management and Division of Mitigation Assessments and Medication Error Surveillance review of the proposed Camzyos REMS Assessment Plan submitted by Bristol Myers Squibb on January 25, 2022. To facilitate further review, please address the following comments in your forthcoming REMS submission on March 16, 2022. These comments should not be considered as final edits to the REMS.

Drug Interaction and (b) (4) Counseling Checklist

- See the attached redlined checklist for additional edits for clarity, including the addition of a warning to pharmacists not to dispense Camzyos until receiving authorization in the instruction section of the form. Some portions of the form, including the reference section with examples of medications or supplements contraindicated or requiring dose adjustment, have been moved to better align with pharmacy workflow.
- Incorporate additional questions to align with Assessment Plan edits to collect metrics related to the number of *Drug Interaction and* (b) (4) *Counseling Checklists* that identified a concurrent contraindicated medication or medication that required a dose adjustment, the source of the medication or supplement, and the action taken after identification.

^a Section 505-1(a) of the FD&CA Act: *FDAAA factor (F)*: Whether the drug is a new molecular entity

3. Appendices

3.1 REFERENCES

1. Cunningham, C., Division of Risk Management Interim Comments on the Proposed Camzyos (mavacamten, NDA 214998) REMS, March 2, 2022, DARRTS ID# 4945947.

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LAURA A ZENDEL
03/09/2022 11:57:31 AM

NDA 214998 Mavacamten

The REMS Assessment plan submitted in the January 25, 2022, Mavacamten REMS Supporting Document has been reviewed and the following general comments are provided. In addition, an updated draft Assessment Plan is provided for the Applicant to use as a basis for future submissions.

- 1) The Agency has determined that (b) (4) are not necessary for this REMS program and references to those can be removed from the Assessment Plan.
- 2) We have identified a key performance indicator (KPI) and an appropriate threshold which is necessary and essential in determining if the REMS is functioning as designed to achieve the goal of mitigating the risk of heart failure due to systolic dysfunction.
 - a. The proposed KPI is the number of prescriptions dispensed with an authorization from the REMS program when the prescription:
 - i. Will be dispensed from a Certified pharmacy
 - ii. Written by a Certified prescriber
 - iii. Written for an Enrolled patient
 - iv. Has a completed Patient Status form that documents an appropriately timed ECHO
 - v. Has a completed the Drug Interaction and Counseling Checklist for Pharmacies (DIC checklist) that documents appropriate actions were taken prior to authorization.

The proposed threshold for the KPI is that 99.9% of dispenses are associated with an approved authorization

- 3) The Agency has updated the Assessment Plan to include not only the number of occurrences for metrics but a proposed appropriate denominator to evaluate the results by. For metrics related to Safe Use Conditions and Compliance, the Agency has proposed definitions of acceptable results.
- 4) Replace all [Tradename] with Camzyos
- 5) If necessary, update your current Assessment Plan metrics based on any program changes to the REMS as recommended in the comments sent on March 2, 2022.
- 6) Use the term risk mitigation authorization for an authorization to dispense as we have included in the Assessment Plan and then you should update the Supporting Document accordingly. Alternatively, propose another term for an issued authorization to dispense and then update the Assessment Plan and Supporting Document accordingly.
- 7) Update your Assessment Plan to include that metrics will be presented for the two previous reporting periods, current reporting period, and cumulatively unless otherwise stated.
- 8) As provided below, in future submissions, provide the Assessment Plan in an outline format rather than a table format.
- 9) Submit the annual REMS Assessment Report in PDF and clean Word documents. Submit tables in the report in excel as a supplement with N and % or other numerators and denominators as separate columns.

The Agency has attempted where possible to utilize the table submitted by the Applicant converting to an outline format and marking additions with underline and deletions with ~~strike through~~. -

9 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

CHARLOTTE T JONES
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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214998
PDUFA Goal Date	April 28, 2022
OSE RCM #	2021-191
Reviewer Names	Courtney Cunningham, PharmD Katherine Hyatt Hawkins Shaw, PhD Kate Heinrich Oswell, M.A.
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Division Director	Laura Zendel, PharmD
Review Completion Date	March 02, 2022
Subject	Evaluation of Proposed REMS
Established Name	Mavacamten
Trade Name	Camzyos
Name of Applicant	Bristol Meyers Squibb
Therapeutic Class	Cardiac Myosin Inhibitor
Formulation(s)	2.5, 5, 10, and 15 mg oral capsules
Dosing Regimen	Starting dose 5 mg daily: may increase 12 weeks after initiation based on PD markers

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1 Introduction

This review evaluates the risk evaluation and mitigation strategy (REMS) amendment on January 25, 2022, for the new molecular entity (NME)^a Camzyos (mavacamten). Bristol Myers Squibb submitted a New Drug Application (NDA 214998) for mavacamten with the proposed indication for the treatment of symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) in adults to improve functional capacity, (b) (4), and symptoms. This application is under review in the Division of Cardiology and Nephrology (DCN). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of mavacamten outweigh the risk of heart failure due to systolic dysfunction.

2 Background

2.1 REGULATORY HISTORY

The following is a summary of the regulatory history for mavacamten (NDA 214998) relevant to this review:

- 08/06/2021: Applicant submitted modeling of exposure-response and pharmacokinetic/pharmacodynamic simulations evaluating different dosing and monitoring protocols in CYP2C19 genotypes in response to the Agency's request on July 14, 2021. During subsequent analysis of this modeling by the Office of Clinical Pharmacology (OCP), it was confirmed that poor CYP2C19 metabolizers have an increased risk of adverse events and would also be at greater risk of systolic dysfunction if a drug that further inhibited the metabolism of mavacamten was administered concomitantly.
- 09/16/2021: The Division of Risk Management (DRM) provided comments and redlined REMS materials to the Applicant on the January 28, 2021, REMS submission.
- 09/30/2016: A Discipline Review Letter was issued noting that prospective CYP2C19 genotyping, and availability of a companion diagnostic may be required for optimizing efficacy and reducing risks for poor CYP2C19 metabolizers.
- 10/07/2021, 10/27/2021, 11/02/2021: The Applicant and Agency engaged in discussion regarding the feasibility and appropriateness of prospective genotyping using a companion diagnostic.
- 11/08/2021: The Applicant submitted a REMS amendment including prospective genotyping as a requirement of the REMS. This constituted a major amendment.
- 11/18/2021: Major amendment acknowledgement letter sent to Applicant: PDUFA goal extended by 3 months to April 28, 2022.

^a Section 505-1(a) of the FD&C Act: *FDAAA factor (F)*: Whether the drug is a new molecular entity

- 01/22/2022, 01/12/2022: The Applicant and the Agency discussed the need to involve stakeholders in the REMS planning to ensure the proposed REMS can be incorporated into practice workflows.
- 01/25/2022: The Applicant submitted a REMS amendment that included a REMS proposal that did not include prospective genotyping requirements.
- 02/04/2022: The Applicant submitted their findings of stakeholders' feedback regarding the REMS.

3 Discussion

At the August 4, 2021, REMS Oversight Committee (ROC) meeting the clinical and REMS review teams proposed a REMS with ETASU for mavacamten to ensure the benefits outweigh the risk of heart failure due to systolic dysfunction (symptomatic left ventricular ejection fraction (LVEF) < 50%) resulting from excessive pharmacologic effect of mavacamten. The proposed REMS requires periodic echocardiographic assessment of LVEF to detect mavacamten-induced depression of ventricular dysfunction early and prevent further deterioration through drug discontinuation or dose adjustment. The ROC concurred with the review team but had concerns regarding drug-drug interactions and the unknown effect of metabolizer status on the potential of adverse events.¹

On August 6, 2021, the Applicant submitted correspondence in response to an Agency request during the midcycle meeting on July 14, 2021 to submit modeling of exposure-response and pharmacokinetic/pharmacodynamic simulations evaluating different dosing and monitoring protocols in CYP2C19 genotypes.² Patients who are CYP2C19 poor metabolizers have higher exposures of mavacamten compared to normal, rapid, and ultrarapid metabolizers. When analyzed by the Office of Clinical Pharmacology (OCP), the risk to patients who were poor CYP2C19 metabolizers was indeed greater than that of normal, rapid, and ultrarapid metabolizers. Poor metabolizers would also be at increased risk of systolic dysfunction if mavacamten was taken concomitantly with a drug that further inhibited mavacamten metabolism.³ A Discipline Review Letter issued on September 30, 2021 noted that prospective CYP2C19 genotyping and availability of a companion diagnostic may be required to use mavacamten and manage risks for patients who are poor CYP2C19 metabolizers.⁴ OCP also expressed concerns regarding the challenges in therapeutic management of mavacamten including an inherent risk from inadvertent drug-drug interactions, including those with over-the-counter products, that are difficult to control in clinical use. DCN has since worked closely with the OCP on determining adequate posology and dosing instructions for drug-drug interactions (DDIs). Continuous discussions between the review team and the Applicant followed, many of which centered around the need for and feasibility of developing a companion diagnostic to prospectively genotype all patients who were going to begin mavacamten therapy. Team members from the Center for Devices and Radiological Health (CDRH) noted that there are no CYP2C19 genotype diagnostics on the market for the purpose of ensuring the safe use of a product, and the Applicant would need to develop a companion diagnostic for mavacamten prior to approval if prospective genotyping is required for safe use of the product. Given that the time required for the Applicant to develop a companion diagnostic would lead to a multi-year delay for patients as well as consideration of the low prevalence of poor CYP2C19 metabolizer phenotype (1-5%

of the US population), DCN worked with OCP to seek other options that do not require prospective genotyping.

With these limitations on availability of prospective genotyping data, OCP conducted additional simulations using available population PK and exposure-response models and explored a new dosing algorithm with increased ECHO monitoring frequency, slower up-titration, and without genotyping. The optimized dosing regimen and ECHO frequency offers a similar risk (measured as percentage of patients with LVEF < 50%) and benefit (measured as percentage of patients with VLVOT gradient < 30mmHg) profile compared to the prospective genotyping regimen. Considering that mavacamten is for symptomatic relief, not reduction of mortality, DCN favored this conservative, universal dosing approach.

In the dosing regimen proposed by OCP and used in the Applicant's proposed label,⁵ the starting dose is 5 mg once daily (Week 0) in all patients irrespective of CYP2C19 genotype. Clinical visits including an echocardiogram are scheduled at Week 4, Week 8, Week 12, and every 12 weeks thereafter. The proposed dosing algorithm allows down-titration only at Week 4 and Week 8, if Valsalva left ventricular outflow tract (VLVOT) gradient is less than 20 mmHg. Similarly, a patient may be eligible for up-titration after 12 weeks (on Week 12, 24, etc.), if VLVOT gradient is (b) (4) 30 mmHg (indicating that desirable efficacy is not reached) and LVEF is (b) (4) 55% (indicating that it is safe to increase dose with available ejection fraction). In addition, the dosing algorithm includes an additional clinical visit with ECHO monitoring 4 weeks following any dose increase or when restarting treatment after temporary discontinuation ensuring safety at the new dose.

Temporary discontinuation is recommended if ejection fraction drops below 50% at any clinical visit. Patients may resume mavacamten at one lower dose level (i.e., 15 to 10 mg; 10 to 5 mg; 5 to 2.5 mg; once daily) if the ejection fraction returns above 50% at an additional visit 4 weeks after the temporary discontinuation. Permanent discontinuation is recommended if a patient experiences 2 incidences of ejection fraction going below 50% at the lowest dose (i.e., at 2.5 mg once daily) at any time during treatment.

The above dosing algorithm and monitoring schedule allows for the safe and effective use of mavacamten by patients regardless of metabolizer status. However, safety concerns lingered regarding DDIs, especially those involving nonprescription medications and supplements. OCP recommended either to avoid concomitant administration or dose reduction of mavacamten based on the expected magnitude of effect. Concomitant administration of mavacamten with a moderate or strong inhibitor of CYP2C19 as well as a strong inhibitor of CYP3A4 are contraindicated. Due to the number of therapies available and magnitude of pharmacological effect, OCP recommendations were to decrease the dose of mavacamten and complete ECHO monitoring at Week 4, Week 12, and every 12 weeks thereafter with concomitant administration of mavacamten with a weak inhibitor of CYP2C19 or moderate inhibitor of CYP3A4.³

To further mitigate the risk of heart failure due to systolic dysfunction because of drug-drug interactions, DRM added screening for drug-drug interactions prior to each dispense as a second objective to the proposed mavacamten REMS. DCN and DRM discussed multiple options to mitigate the

risk of DDIs contributing to heart failure due to systolic dysfunction and concluded that screening for DDIs should be done by the healthcare provider prior to treatment initiation and with each clinical visit, i.e., with every *Patient Status Form* completion. Additionally, the pharmacist should also screen for DDIs prior to each dispense to include any medications that may have been recently added or purchased between visits. To accomplish this objective, DRM added a *Drug Interaction and (b) (4) Counseling Checklist for Pharmacies* as a REMS material to ensure patients' prescription and over the counter medications and supplements are reviewed by the certified pharmacy for drug-drug interactions prior to each dispense to decrease the probability of drug-drug interactions.

While DRM and DCN agreed with the Applicant's proposal that a healthcare provider could name a delegate, (b) (4)

(b) (4) DRM and DCN agree to allow a designee that is a licensed medical professional in the practice, (RN, NP, PA, RPh) named by the certified healthcare provider, to complete specific tasks in the Camzyos REMS including completing Patient Enrollment Forms, Patient Status Forms, and counseling patients. (b) (4) ensures practitioners familiar with patient counseling, reading echocardiogram reports, and DDI screening are performing these tasks in the Camzyos REMS.

4 Comments for the Applicant

The following comments and attached redlined Camzyos Risk Evaluation and Mitigation Strategy (REMS) materials are based on our preliminary review of the proposed REMS submitted by Bristol Myers Squibb on January 25, 2022. To facilitate further review, please address the following comments and resubmit your complete REMS (clean and redlined Word versions and clean pdf versions of the REMS Document and all materials) as an amendment by March 16, 2022. These comments should not be considered as final edits to the REMS.

General Comments and Information Requests:

- In the February 4, 2022, submission, you propose dispensing a 35-day supply of mavacamten. We have two concerns with this approach: 1) many commercial insurance plans pay for a 30-day supply of outpatient medications and 2) the proposed package size is a 30-count bottle leading to inefficiencies and potential for drug waste at the pharmacy. Please provide additional rationale for maintaining a 35-day supply of mavacamten to address these concerns.
- Please elaborate on the authorization process for a prescription at certified pharmacies. How does the pharmacist know they can dispense, for example, does the pharmacist receive an authorization number?

- (b) (4)
(b) (4) We recommend that healthcare providers

would be able to enter VLVOT and LVEF values, current dose and duration, and any drug interactions and dose changes, then receive information regarding when the next echocardiogram is due and if the healthcare provider can increase the dose of mavacamten.

- In the next submission, incorporate the conditionally acceptable tradename and logo into all REMS materials.
- (b) (4)
(b) (4) we do agree that healthcare providers may have a “Designee” that is selected by the certified healthcare provider and is a licensed registered nurse, pharmacist, or physician assistant due to the complexities of dosing, ECHO monitoring, and drug-interaction monitoring for mavacamten. We have provided a redlined *Designee Enrollment Form*, based on the proposed (b) (4)
(b) (4)
- Due to concerns regarding drug-drug interactions with inhibitors of CYP2C19 and CYP3A4 that could contribute to heart failure due to systolic dysfunction, we have included a requirement that healthcare providers screen for drug-drug interactions as one of the objectives of the REMS. We have also included a *Drug Interaction and* (b) (4) *Checklist* as a REMS material; this requires dispensing pharmacists to conduct a screening of all prescription and nonprescription medications and supplements for drug-drug interactions, and counsel the patient. We have included a draft *Checklist*. The Pharmacist Portal should be designed to allow for online completion and submission of the *Drug Interaction and Counseling Checklist*, along with capabilities for pharmacists to see the information on the *Patient Status Form* and provide a hard stop on dispensing if a contraindicated drug or drug that requires a decrease in mavacamten dose is noted on the *Checklist*.
- A complete list of attestations is under internal review and will be provided with Agency comments after the next submission of the REMS.
- As “healthcare providers” is used predominantly in the submitted REMS Document, all materials must align with that terminology. Align the use of “healthcare providers” instead of (b) (4) throughout the REMS Document and all materials.
- As the patient being enrolled in the REMS may not have already had a baseline echocardiogram at the time of enrollment, questions pertaining to all echocardiogram results have been incorporated into the *Patient Status Form*. Healthcare providers can now complete the *Patient Enrollment Form* with the patient, order an echocardiogram, then record the results on the *Patient Status Form* when they receive them. This will allow healthcare providers to better incorporate the REMS into daily practice.
- All REMS materials should be named (b) (4)
(b) (4) “Patient Brochure” and “Program Overview.”

- [REDACTED] (b) (4)
[REDACTED] . As such, this should be removed from the REMS as increased monitoring/dose decreases are at the provider's discretion.
- Redlined versions of the REMS Document and all materials are attached. We have made numerous edits for content and clarity. Please address all edits and comments from the Agency in your redlined materials and cover letter if necessary.
- All REMS materials must be revised to be consistent with the final approved labeling and resubmitted for review.

REMS Document

- The REMS Document lists MyoKardia, Inc. as the application holder. If this is now held by Bristol-Myers Squibb, please edit and align all materials with Bristol Myers Squibb information.
- The Agency's thinking regarding how to write REMS goals is changing to focus the REMS goals to align with public health prevention goals: primary prevention (prevent), secondary prevention (screen), tertiary prevention (manage), and/or informed benefit-risk decision making. [REDACTED] (b) (4)
[REDACTED] has been removed from the goal and will be used as a tool to accomplish the objectives of the REMS. The objectives of the REMS Goal have been updated to incorporate screening by healthcare providers and pharmacists for drug-drug interactions. The new goals and objectives of the REMS are as follows:

The goal of the Camzyos Risk Evaluation and Mitigation Strategy (REMS) Program is to mitigate the risk of heart failure due to systolic dysfunction.

Objectives:

- Monitor for detections of heart failure due to systolic dysfunction with periodic echocardiograms
- Screen for drug interactions prior to each dispense
- All sections of the REMS Document must be evenly spaced in this resubmission. Remove extra space where necessary, ensure all REMS materials are the same color/shade of blue.
- Include screening for drug-drug interactions in the healthcare providers' responsibilities, and screening and documentation in the certified pharmacy's responsibilities to mitigate the concern of drug-drug interactions, especially in patients who are poor CYP2C19 metabolizers.
- We have incorporated the 35-day dispense into the timelines in the document. If 35-day dispenses will not be possible for all patients, these must be recalculated based on a 30-day dispense.

REMS Supporting Document

- Align the Supporting Document with edits made to the REMS Document (i.e., removal of (b) (4), need to inform healthcare provider of intercurrent illness/arrhythmias, etc.).

Healthcare Provider Enrollment Form

- Add an option for “geneticist” into the healthcare provider specialty choices.
- In the pdf version, include box and formatting around “Healthcare Provider Responsibilities.”

Healthcare Provider Designee Enrollment Form (b) (4)

- We have renamed this form to distinguish the designee from other responsibilities. The designees do not need to attest to any actions since the certified healthcare provider maintains responsibility in the REMS.
- Replace the term (b) (4) with “Designee” to align with the Agency’s current thinking on terminology for designees in REMS programs.
- The ability to name a Designee should be incorporated into the healthcare provider portal of the REMS Website.
- In the final submission, this material should be appended to the Supporting Document.

Patient Enrollment Form

- Add a question in the form to note if the patient has participated in a clinical trial and will now be enrolling in the REMS on a dose that may be higher than expected for a patient new to the REMS.
- Remove the (b) (4)
(b) (4)
(b) (4)
- Patients will be receiving the *Patient Brochure* at clinic visits and with each dispense. (b) (4)
(b) (4)
(b) (4)

Pharmacy Enrollment Form

- Remove the pharmacy’s DEA number from this form, as mavacamten is not expected to be a controlled substance. The NPI number will suffice.

- We have included completion of the *Drug Interaction and Counseling Checklist for Pharmacies* in the responsibilities portion of the form.

Program Overview

- The *Program Overview* has been edited to include screening for drug-drug interactions by healthcare providers and pharmacists, as well as edits to include monitoring schedules for quick reference for stakeholders. It has also been edited to align with the REMS Document.

Education Program for Healthcare Providers and Pharmacies

- We have aligned the content of the *Education Program* with the current label and REMS Document. The *Education Program* should focus on the REMS risk and program information and not contain any promotional content.
- Choose graphics/icons with caution. Ensure all graphics/icons align with the content of the slide. The shield with checkbox graphic must be changed, as it does not align with the messages it is used with and seems to promote that the content is acceptable. (b) (4)
- (b) (4) slides can be deleted. (b) (4) are incorporated into the (b) (4) and other information in the REMS presented in the earlier slides.
- Revise the formatting of the slides. Widen the margins on the sides so that written content does not have to stretch so far across the page, as that makes it more difficult to read. All content on slide does not need to be boxed. Consider shading to call out information if there are multiple boxes on a slide.
- Headings should be concise and align with content. See redlined edits for suggestions.
- Dosing/monitoring/titration/drug interaction/down titration graphics should be incorporated.
- Use “once daily” (b) (4) in slides.
- Thumbnails of the forms are not needed on the slides as the content is too small to see and does not add much to the information on the slide. Consider making links to the REMS materials instead for the online versions.
- The (b) (4), and ‘Patient Status Form Submission’ chart has a lot of information compressed into it. Split the timeline out to make two charts, one for year 1 and one for year 2+. These should be on their own slide. Footnotes for the chart should have a normal font size so they are readable.
- Include the need for drug-drug interaction screening by healthcare providers and pharmacists, as this will be viewed by both stakeholder groups.

- Add a few vignettes or scenarios for healthcare providers and pharmacists making decisions based on patient situations. Include scenarios for the following: typical dosing and discontinuing drug and subsequent up-titration. Include details as to what would occur at clinical visits and dosing and monitoring changes.

Healthcare Provider Knowledge Assessment

- Please see the redlined document for edits to the questions for clarification and to align with the REMS materials, [REDACTED] (b) (4)
- We have provided a question regarding dose adjustments due to a drug-drug interaction.

Pharmacy Authorized Representative Knowledge Assessment

- Please see the redlined document for edits to include the *Drug Interaction and Counseling Checklist for Pharmacies* and to emphasize REMS information that is most important to pharmacists.
- We have provided an alternative question that focuses on the dispensing of mavacamten has replaced [REDACTED] (b) (4) and added a sample question regarding dispensing limits to focus on knowledge needed for those dispensing mavacamten.

Patient Brochure

- Box or call out several common symptoms of heart failure to remind patients to be aware of the risk and call their healthcare provider if they experience these symptoms.
- Revise the monitoring graphic to better illustrate when patients need to have echocardiograms completed.
- We made edits to shorten the content and rearranged the information to provide the most important information up front, including the risk heart failure, symptoms of heart failure and drug interaction risk.
- We recommend widening the margins to improve ease of reading the document.
- The box that highlights drug interactions should be modified so that the visual representation shows rows instead of columns to visually balance out the content. For example, 'Over the Counter' would be on the left with the examples on the right in its own row. Names of medicines could appear vertically within the row. The 'Prescriptions' would be in a row underneath the 'Over the Counter' row.

- [REDACTED] (b) (4)

Patient Status Form

- The echocardiogram monitoring schedule should be presented in a clear, concise format, and include a schedule for titration after dose decrease due to drug interaction. The schedule needs to be included only one time but should be prominent and easy to follow.
- Several questions have been added so the form may be used for new patients, incorporate documentation for drug-drug interaction screening, and to assist providers in monitoring dosing changes by the addition of a question on VLVOT.

Drug Interaction and Counseling Checklist for Pharmacies

- We have provided this checklist to mitigate the risk of patients using mavacamten with other prescriptions, over the counter medications, or supplements that would interact with mavacamten and increase the risk of heart failure. This checklist is to be completed and submitted to the REMS by the dispensing pharmacist. It also serves as a final hard stop in the event a patient is taking a contraindicated medication or a medication that requires a dose adjustment of mavacamten. If so, the dispensing pharmacist must contact the provider and not dispense mavacamten until the contraindicated medication is discontinued or the dose of mavacamten adjusted appropriately.
- To fill out this checklist properly, the Pharmacy Portal must allow pharmacists to access information on the *Patient Status Form* to ensure the dose of mavacamten is correct and the patient is authorized to continue mavacamten therapy.
- Align the examples of heart failure symptoms from the *Patient Brochure* with the list on this checklist.

REMS Program Website

- Align all REMS materials on the website with the print versions.
- Apply our comments on the REMS materials to similar presentations in the REMS Website screenshots. Final website screenshots should also incorporate these changes.
- Incorporate the *Drug Interaction and Counseling Checklist* into the REMS website on the pharmacy page and resources page.
- (b) (4) is not a part of the REMS and must be removed from the REMS website.

- Remove (b) (4) Pharmacists will reach the portal through the REMS website.
- Indication and adverse event reporting information (b) (4)
- Please see other edits on the REMS website.
- We remind you to submit a complete set of updated REMS website screenshots showing all content and functionality of the website, including online education, knowledge assessment and enrollment. This would include the data fields to complete, and the information that pops up for the provider to read.

Website Stakeholder Portals

- We have not commented specifically on your website portal as it is still under development and is incomplete. Revise the portal to incorporate all aspects of the REMS Document including safe use conditions including the *Patient Status Form* and *Drug Interaction and Counseling Checklist*. In addition, the designee should be incorporated as appropriate within the prescriber dashboard. The screenshots should also show all portal capabilities in complete pages and content so a reviewer could follow how each activity takes place. For example, how a healthcare provider would enroll a patient or complete a patient status form and how a pharmacist would find a patient and complete required tasks to be able to dispense drug.
- These portals must also show the popups when a “hard stop” in prescribing or dispensing occurs. For example, submit screenshots of the hard stop when a healthcare provider/designee attempts to submit a *Patient Status Form* when a patient has an LVEF <50% but the provider/designee does not choose the “dose interruption” option on the form. Screenshots of popups and hard stops that occur in the pharmacy portal must also be submitted, such as those for occasions when a *Patient Status Form* or *Drug interaction and Counseling Checklist* is not submitted, or when there is a drug interaction noted on the *Checklist*, but no outcome is documented.

REMS Assessment Plan

- Comments will be forthcoming.

5. References

1. Minutes from the August 4, 2021 Mavacamten REMS Oversight Committee Meeting
2. Bristol-Myers Squibb. Response to Clinical Pharmacology Information Request Mavacamten (NDA 214998).

3. Bende, G. et al., Office of Clinical Pharmacology Review of Mavacamten (NDA 214998) Amendment, January 28, 2021 DARRTS ID#12355403.
4. Childers A. Discipline Review Letter for Camzyos (mavacamten) (NDA 214998) DARRTS ID 12355403.
5. Bristol-Myers Squibb Draft Camzyos (mavacamten NDA 214998) Label January 18, 2022 Submission

84 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214998
PDUFA Goal Date	January 28, 2022
OSE RCM #	2021-191
Reviewer Name(s)	Courtney Cunningham, PharmD Kate Heinrich Oswell, M.S.
Team Leader	Laura Zendel, PharmD, BCPS
Review Completion Date	Sept 15, 2021
Subject	Evaluation of Proposed REMS
Established Name	Mavacamten
Proposed Trade Name	Camzyos
Name of Applicant	Myokardia, Inc.
Therapeutic Class	Cardiac Myosin Inhibitor
Formulation(s)	2.5, 5, 10, and 15 mg oral capsules
Dosing Regimen	Starting Dose 5mg daily; may increase or decrease in 12 weeks after initiation based on PD markers

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1 Introduction

This review evaluates the proposed risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)^a Camzyos (mavacamten). Myokardia, Inc. submitted a New Drug Application (NDA 214998) for mavacamten with the proposed indication for the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adults to improve functional capacity, (b) (4) and symptoms. This application is under review in the Division of Cardiology and Nephrology (DCN). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of mavacamten outweigh the risk of heart failure due to systolic dysfunction.

2 Background

2.1 REGULATORY HISTORY

The following is a summary of the regulatory history for mavacamten (NDA 214998) relevant to this review:

- 04/27/2016: Agency granted Orphan designation for the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adults to improve functional capacity, (b) (4) and symptoms
- 07/12/2020: Applicant informed by clinical review team at pre-NDA meeting that a REMS for mavacamten was needed to mitigate the risk of heart failure
- 07/22/2020: Agency granted Breakthrough Therapy designation for the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adults to improve functional capacity, (b) (4) and symptoms
- 10/06/2020: An informal teleconference meeting was held with Myokardia, the DCN clinical review team, and DRM to discuss Myokardia's proposal for (b) (4) REMS. The DCN clinical review team emphasized the need for a REMS ensuring ECHO monitoring was performed.
- 01/28/2021: NDA 214998 submission with the proposed indication for the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adults to improve functional capacity, (b) (4) and symptoms received
- 07/14/2021: A Mid-cycle communication meeting was held between the Agency and Myokardia via teleconference. The Agency informed Myokardia that a REMS was necessary to ensure the benefits of Myokardia outweigh the risk of heart failure due to systolic dysfunction. DRM

^a Section 505-1(a) of the FD&CA: *FDAAA factor (F): Whether the drug is a new molecular entity*

informed Myokardia that comments on to the proposed REMS would be forthcoming once Agency meetings with management were completed.

3 Comments for the Applicant

The following comments and attached redlined Mavacamten Risk Evaluation and Mitigation Strategy (REMS) materials are based on our preliminary review of the proposed REMS submitted by Myokardia on January 28, 2021. To facilitate further review, please address the following comments and resubmit your complete REMS as an amendment within 15 business days of receipt. These comments should not be considered as the final edits to the REMS.

General Comments and Information Requests:

- Further changes are necessary for the REMS to be acceptable. See comments below and attached redlined materials. All versions of the materials should be aligned (pdf and Word versions).
- We note that your proposed labeling is currently under review. All REMS communication materials must be revised to be consistent with the final FDA approved labeling and resubmitted for review.
- All REMS program information must reflect what is in the REMS Document. Align all materials with edits made to the REMS Document.
- Phone numbers used by the REMS may not link to information that is promotional.
- Align the ECHO monitoring schedule on the REMS Document and all materials with any edits or labeling sent by the Agency. Update the limitation to 30-day supply dispense of mavacamten, as opposed to the dispensing limitations as proposed. (b) (4)

[REDACTED]

[REDACTED] As pharmacies must contact the REMS prior to dispensing to ensure prescriber certification, patient enrollment, and that a current PSF or Patient Enrollment form is on file for the patient prior to dispensing, a dispensing limitation is a more feasible option. By limiting to a 30 day dispense throughout the use of mavacamten, the REMS can better ensure patients do not receive excess medication in the event of dose changes or therapy discontinuation. Changes to the Patient Status Form (PSF) schedule: in order to ensure that patients do not experience excessive time off drug due to delays in ECHO monitoring or PSF submission, but still adhere to the necessary ECHO monitoring schedule, the calculation of the PSF submission should be as follows:

[REDACTED] (b) (4)

(b) (4)

- Remove [REDACTED] (b) (4)
- Provide further clarification on how pharmacies obtain an authorization to dispense prior to dispensing in the supporting document.
- What will the processes and procedures be if mavacamten is dispensed to patients who are inpatient or in closed healthcare systems such as the VA or Kaiser Permanente? Are specialty pharmacies the only dispenser expected for outpatient use? If requirements are different, e.g., for inpatient pharmacies, a separate section in the REMS document and separate enrollment forms may be considered.
- Will subjects from studies continue on mavacamten once they have completed the study? If so, how will these patients be transitioned into the REMS, as they may come into the REMS on a stable dose?
- Provide a proposed implementation timeline following approval.

REMS Document

- Change the REMS Goal to: The goal of the [TRADENAME] Risk Evaluation and Mitigation Strategy (REMS) Program is to mitigate the risk of heart failure due to systolic dysfunction.
 - Objective 1:
Monitor for detection of heart failure due to systolic dysfunction with periodic echocardiograms.”
- Clarify the meaning of [REDACTED] (b) (4)
- Where noted, elaborate on whether Myokardia, the REMS program, or the dispensing pharmacy will contact the prescriber if the Patient Status Form has not been submitted.

REMS Supporting Document

- On Page 13, further explain how the pharmacies “Obtain authorizations to dispense each prescription.” Include how the authorization is tracked and what happens if the prescription is not authorized.
- Update entire document with current attestations on the attestations document and align with the REMS Document.

- Include pharmacy and wholesaler/distributor contracting information in the supporting document, not the REMS Document, as contracting is not a requirement of the REMS.
- Attach the proposed Adverse Event Reporting Form to the Supporting Document for the next submission and elaborate on how the data obtained from the form will be used to inform the REMS.

Healthcare Provider Enrollment Form

- Update the form with the current attestations for stakeholders using the attestations on the attached Attestations Document.
- Remove extemporaneous information from the form for brevity and clarity.
- As mavacamten (b) (4), remove the (b) (4) on the form (b) (4).
- Revise the introduction and the instructions to keep this form simple.
- The font size of the data field names on PDF version of this form needs to be increased throughout.
- Under Specialty, add Electrophysiology and Geneticist as options.

Patient Enrollment Form

- Update the form with the current attestations for stakeholders using the attestations on the attached Attestations Document.
- Reformat the prescriber section's ECHO queries to align with the questions to prescribers on the Patient Status Form to allow for continuity of information provided to the REMS.

- (b) (4)
- Add options for (b) (4) including "Neutral" and "Prefer not to Say" for inclusivity for all patients.
- Remove information not needed on the form to improve clarity for patients.
- On the pdf version of the form, the font size of data field names must be increased throughout.
- As the healthcare provider (b) (4)

(b) (4)
it should be deleted from the form.

Pharmacy Enrollment Form

- Update the form with the current attestations for stakeholders using the attestations on the attached Attestations Document.
- Use NPI to identify the pharmacy, (b) (4) as NPI is a more current identifier of pharmacies.
- Move pharmacy authorized representative contact information above the attestations.
- Revise the introduction and the instructions to keep this form simple.
- The font size of the data field names on PDF version of this form needs to be increased throughout.

REMS Program Overview

- Update as per attached redlined edits so this material may be used as the pharmacy education material instead of the slide deck focused on the educational needs of healthcare providers.
- Add symptoms of heart failure due to systolic dysfunction to Page 2.
- Align with stakeholder requirements as per the updated REMS Document.
- Retitle the (b) (4) section to “Resources” as it includes materials that are not part of the REMS.

Education Program for Healthcare Providers

- Edit the Education for Healthcare providers slides to increase brevity and clarity by including less text per slide. Also consider using colors, text boxes, or other layouts to make the content easier to read and understand.
- Ensure all content aligns with labeling and other REMS programmatic changes including the recommended changes to the REMS goal
- Include visual timelines for ECHO monitoring schedule
- Remove (b) (4)
- Update dispensing limits (slide 28)
- Add content regarding the impact of drug interactions and CYP2C19 metabolizer status in the [TRADENAME] Overview section

Healthcare Provider Knowledge Assessment

- Remove the unnecessary information at the top of the Knowledge Assessment for brevity and clarity.
- Replace Questions 1 and 10 with the edits provided in the attached redlined materials for a more comprehensive test of necessary knowledge to be certified in the REMS.
- Ensure all other questions align with labeling and the REMS document.

Patient Brochure

- Remove (b) (4)
- Remove (b) (4) as the guide’s target audience is patients.
- Streamline the content and limit this material to one page front and back (pdf formatted version).
- Edit to provide concise information related to the risk of heart failure due to systolic dysfunction and the requirements of the REMS.

Patient Status Form

- The font size of the data field names on PDF version of this form needs to be increased throughout.

- Update the questions in the Patient Status box as follows to improve information received by the REMS:



REMS Program Website

- Submit Word and pdf screenshots of the REMS website for review, ensuring all materials are aligned with print versions. Prior to approval, screenshots demonstrating full functionality of the website must be submitted to the Agency. To facilitate our review, you may submit the screenshots as wire frames to demonstrate the functionality and include the content separately to be incorporated at a later date. If you have proprietary screenshots, for example, content past a login screen, include them as an appendix within the supporting document.
- (b) (4) can be removed from the website landing page. This information is contained in the REMS details provided on subsequent pages.
- Apply our comments on the REMS materials to similar presentations in the REMS Website screenshots. Final website screenshots should also incorporate these changes.
- Submit a complete set of updated REMS website screenshots showing all content and functionality of the website. If online education and/or enrollment is an option, you must submit a screenshot(s) of what the new window(s) would look like as part of the functionality of your website submission. This would include the data fields to complete, and the information that pops up for the provider to read.
- To ensure real-time access to mavacamten patient, prescriber, and pharmacy information, and verification of safe use conditions, a website portal is needed as part of the REMS program implementation. The website portal is considered a part of the mavacamten REMS. We must review all screenshots showing the functionality of the portal. Submit screenshots for the website portal.

REMS Assessment Plan

Comments on the assessment plan will be forthcoming.

88 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

COURTNEY A CUNNINGHAM
09/16/2021 08:11:25 AM

KATE H OSWELL
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LAURA A ZENDEL
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